
Statistical Analysis Plan

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A 52-Week, Multicentre, Randomized, Double-blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β_2 - Agonist (STRATOS 2)

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A & R Statistician



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Study Statistician



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Global Product Statistician



	PAGE
TITLE PAGE.....	1
SIGNATURE OF STUDY STATISTICIAN.....	2
SIGNATURE OF STUDY STATISTICIAN.....	3
SIGNATURE OF GLOBAL PRODUCT STATISTICIAN.....	4
TABLE OF CONTENTS.....	5
LIST OF ABBREVIATIONS.....	9
AMENDMENT HISTORY.....	11
1. STUDY DETAILS.....	12
1.1 Study objectives.....	12
1.1.1 Primary objective.....	12
1.1.2 Secondary objectives.....	13
1.1.3 Other secondary objectives.....	13
1.1.4 Safety objectives.....	14
1.1.5 Exploratory objectives.....	15
1.2 Study design.....	15
1.3 Number of subjects.....	19
2. ANALYSIS SETS.....	19
2.1 Definition of analysis sets.....	19
2.1.1 Efficacy analysis set.....	20
2.1.2 Safety analysis set.....	20
2.1.3 PK analysis set.....	21
2.1.4 PRO analysis set.....	21
2.2 Violations and deviations.....	21
3. PRIMARY AND SECONDARY VARIABLES.....	22
3.1 General Definitions.....	22
3.1.1 Definition of baseline.....	22
3.1.2 FE _{NO}	23
3.1.3 Absolute and percent change from baseline.....	24
3.1.4 Reversibility.....	24
3.1.5 Visit and period windows.....	24
3.2 Calculation or derivation of efficacy variables.....	27
3.2.1 Exacerbation rate.....	27
3.2.2 Proportion of subjects with ≥ 1 asthma exacerbation during 52 weeks of treatment.....	28
3.2.3 Time to first exacerbation.....	28

3.2.4	Annual rate of asthma exacerbations that are associated with an ER or UC visit or a hospitalisation.....	28
3.2.5	Forced expiratory volume in 1 second	29
3.2.6	Forced Vital Capacity and Forced Expiratory Flow at 25-75%	29
3.3	Calculation or derivation of patient reported outcome variables.....	30
3.3.1	Asthma symptom score	31
3.3.2	Rescue medication use	32
3.3.3	Nights with awakening due to asthma	32
3.3.4	Home peak expiratory flow (morning and evening)	32
3.3.5	Asthma Control Questionnaire (ACQ-6)	32
3.3.6	Asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)	33
3.3.7	European quality of life-5 dimensions-5 levels (EQ-5D-5L).....	34
3.3.8	Health care resource utilization	35
3.3.9	The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ).....	35
3.3.10	Clinical global impression of change (CGIC)	37
3.4	Calculation or derivation of safety variable(s)	38
3.4.1	Adverse events.....	38
3.4.2	Safety topics of special attention	39
3.4.3	Laboratory variables	39
3.4.4	dECGs	40
3.4.5	Physical examination	40
3.4.6	Vital signs.....	40
3.4.7	Medical History	41
3.4.8	Calculations or derivation of Pharmacokinetic and Immunogenicity variables.....	41
4.	ANALYSIS METHODS.....	42
4.1	General principles	42
4.1.1	Testing strategy for primary and key secondary objectives	43
4.1.2	Sensitivity analyses.....	46
4.2	Analysis methods	47
4.2.1	Subject disposition, demography data and subjects characteristics.....	47
4.2.2	Prior and Concomitant Medications	48
4.2.3	Exposure and Compliance.....	48
4.2.4	Analysis of the primary variable.....	49
4.2.4.1	Subgroup analyses	50
4.2.4.2	Supportive analysis of the primary variable using adjudicated data.....	51
4.2.5	Analysis of key secondary variable(s)	51
4.2.5.1	Lung Function.....	51
4.2.5.2	Asthma symptoms.....	53
4.2.5.3	Asthma specific health-related quality of life.....	53
4.2.5.4	ACQ-6 defined asthma control.....	54

4.2.6	Analysis of other secondary variables.....	54
4.2.6.1	Proportion of subjects with ≥ 1 asthma exacerbation	54
4.2.6.2	Time to first asthma exacerbation.....	55
4.2.6.3	Emergency room or urgent care visits and hospitalisations due to asthma.....	55
4.2.6.4	Health care resource utilization and productivity loss due to asthma.....	55
4.2.6.5	WPAI-CIQ.....	56
4.2.6.6	Nights with awakening due to asthma	56
4.2.6.7	Rescue medication use	56
4.2.6.8	Home PEF (morning and evening)	56
4.2.6.9	European quality of life-5 dimensions-5 levels (EQ-5D-5L).....	56
4.2.7	Safety and tolerability	57
4.2.7.1	Adverse events.....	57
4.2.7.2	Laboratory data.....	58
4.2.7.3	dECGs	59
4.2.7.4	Physical Examination.....	59
4.2.7.5	Vital Signs	60
4.2.7.6	Weight and BMI	60
4.2.7.7	Analysis of Immunogenicity variables.....	60
4.2.8	Analysis of pharmacokinetics.....	62
4.2.9	Exploratory analyses	62
4.2.9.1	Baseline FE _{NO} levels as predictive biomarker	62
4.2.9.2	Biomarkers associated with up-regulation of IL-13	63
4.2.9.3	Onset of treatment effect.....	63
4.2.9.4	Deoxyribonucleic acid collected for future exploratory research.....	64
5.	INTERIM ANALYSES	64
6.	CHANGES OF ANALYSIS FROM PROTOCOL	65
7.	REFERENCES	65

LIST OF APPENDICES

Appendix A	Analysis Windows for EQ-5D	66
Appendix B	Accounting for Missing Data	68

LIST OF TABLES

Table 1	Estimated power based on biomarker positive population	19
Table 2	Disallowed medications considered to be important protocol deviations	22
Table 3	Visit windows.....	25
Table 4	AQLQ(S) +12 Domains	34
Table 5	Vital signs reference ranges	40
Table 6	Approach to incomplete diagnosis dates for medical history	41
Table 7	Analysis windows for EQ-5D	66
Table 8	Treatment arms used to calculate imputation rate, by reason for withdrawal.....	71
Table 9	Treatment arms used to calculate imputation rate, by reason for discontinuation of treatment.....	72
Table 10	Summary of analyses by estimands.....	74

LIST OF FIGURES

Figure 1	Study flow chart	18
Figure 2	Hierarchical Testing strategy	44

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AAER	Annual Asthma Exacerbation Rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized Prefilled Syringe
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BD	Bronchodilator
CGIC	Clinical Global Impression of Change
CSR	Clinical Study Report
CTD	Common Technical Document
DAE	Discontinuation of Investigational Product due to Adverse Event
dECG	Digital Electrocardiogram
DL	Direct Likelihood
DNA	Deoxyribonucleic Acid
DPP-4	Dipeptidyl Peptidase-4
DRMI	Dropout Reason-Based Multiple Imputation
eCRF	Electronic Case Report Form
ER	Emergency Room
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions - 5 Levels
FEF _{25-75%}	Forced Expiratory Flow at 25-75% of the forced vital capacity
FE _{NO}	Fractional Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FWER	Familywise Error Rate
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GGT	S-Gamma-glutamyl transpeptidase
HbA1c	Glycosylated Haemoglobin
ICS	Inhaled Corticosteroids
IL-13	Interleukin-13
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LABA	Long-Acting β_2 -Agonist
LLOQ	Lower Limit of Quantification
MACE	Major adverse cardiac events
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Antibodies
NB model	Negative Binomial Model
NC	Not Calculable
NQ	Non-quantifiable
OAE	Other Significant Adverse Event
PEF	Peak Expiratory Flow
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Device Agency
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SIDES	Subgroup Identification based on Differential Effect Search
SMQ	Standardised MedDRA Query
TBL	Total Bilirubin
UC	Urgent Care
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

AMENDMENT HISTORY

Date	Brief description of change
22 Jan 2016	Updated to be consistent with STRATOS1 SAP and also as a result of comments on the STRATOS1 (D2210C00007) Blind Data Review. Updates have also been made to implement changes as a result of the CSP amendment no. 3 and updated CSP dated the 8 th October 2015
20 Feb 2017	Updated to add FAS-Japan population following local Japan CSP amendment. Updated with Appendix B : Accounting for missing data. Include eosinophils and previous exacerbations subgroups, and additional adverse event summaries. Medication tables have been updated.
12 Jun 2017	Updated to amend testing strategy to reflect the biomarker positive population as the primary population. Additional information added regarding the options to be used within the PROC MIXED model for key secondary endpoints.
10 Aug 2017	Updated to amend derivation of the offset variable used in the primary analysis to exclude days a subject experienced an exacerbation and the subsequent 7 days.
09 Oct 2017	Updated to include details of FE _{NO} data, add additional sensitivity analysis, remove partial DRMI analysis from Appendix B .
16 Oct 2017	Updated to include information on how to deal with subjects enrolled into the study more than once. Remove algorithm for FE _{NO} and refer to details within the eRT Quality Guidelines instead.

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D2210C00008. The SAP describes the statistical analyses specified in the clinical study protocol (CSP) in more detail; any changes with regards to what is already specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
<p>To evaluate the effect of tralokinumab 300 mg administered every 2 weeks compared with placebo on the annualised asthma exacerbation rate (AAER) in two populations:</p> <p>Biomarker positive population: Subjects in the all subject population meeting the baseline criteria for biomarker positive population specified in Section 4.1 (Primary population)</p> <p>All subjects: Adult and adolescent subjects with the potential to receive 52 weeks of IP with asthma that is inadequately controlled with inhaled corticosteroid (ICS) plus long-acting β2-agonist (LABA) (Secondary population)</p>	<p>Primary outcome variable: The AAER up to Week 52.</p> <p>Primary outcome measure: Asthma exacerbation rate reduction.</p> <p>An asthma exacerbation is defined by a worsening of asthma requiring:</p> <ul style="list-style-type: none"> • Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids. • An emergency room (ER) or urgent care (UC) visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (as per the above). • An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

1.1.2 Secondary objectives

Key Secondary Objectives:	Outcome Measures:
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to lung function	<p>Key outcome variable: Percent change from baseline in pre-dose/pre-bronchodilator (BD) Forced Expiratory Volume in 1 second (FEV₁).</p> <p>Key outcome measure: Percent difference vs. placebo at Week 52.</p>
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to asthma symptoms	<p>Key outcome variable: Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary)</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52.</p>
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to asthma specific health-related quality of life	<p>Key outcome variable: Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older total score (AQLQ (S) + 12).</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52.</p>
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to Asthma Control Questionnaire-6 (ACQ-6) defined asthma control	<p>Key outcome variable: Change from baseline in ACQ-6</p> <p>Key outcome measure: Mean difference vs. placebo at Week 52.</p>

1.1.3 Other secondary objectives

Other Secondary Objectives:	Outcome Measures:
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to other endpoints associated with asthma exacerbations	<ul style="list-style-type: none"> Time to first asthma exacerbation. Proportion of subjects with ≥ 1 asthma exacerbation.
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to emergency room visits, urgent care visits and hospitalisations due to asthma	<ul style="list-style-type: none"> AAER associated with an ER, UC visit or a hospitalisation.
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards pre-dose and post BD FEV ₁	<ul style="list-style-type: none"> Pre-dose/post-BD FEV₁.
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to health related quality of life.	<ul style="list-style-type: none"> European Quality of Life - 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L).

1.1.3 Other secondary objectives

Other Secondary Objectives:	Outcome Measures:
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to health care resource utilization and productivity loss due to asthma	<ul style="list-style-type: none"> • Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire (WPAI+CIQ). • Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).
To assess the effect of tralokinumab compared with placebo in the two subject populations with regards to other measurements of asthma symptoms and asthma control	<ul style="list-style-type: none"> • Rescue medication use. • Home peak expiratory flow (PEF) (morning and evening). • Night-time awakening due to asthma.
To evaluate the pharmacokinetics and immunogenicity of tralokinumab	<ul style="list-style-type: none"> • Pharmacokinetic (PK) parameters: C_{trough} • Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies (ADA) and characterization of their neutralizing potential.

1.1.4 Safety objectives

Safety Objectives:	Outcome Measures:
To evaluate the safety and tolerability of tralokinumab.	<ul style="list-style-type: none"> • Adverse Events(AE)/Serious Adverse Events (SAE) • Vital signs • Digital electrocardiograms (dECG) • Clinical chemistry/haematology/urinalysis • Physical examinations

1.1.5 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
To explore FE _{NO} , and other biomarkers that may be associated with up-regulation of Interleukin-13 (IL-13), as predictive biomarkers for treatment of tralokinumab	Key outcome variable: <ul style="list-style-type: none"> • The AAER up to Week 52 (key variable) Other outcome variables: <ul style="list-style-type: none"> • Percent change from baseline in pre-dose/pre-BD FEV1 • Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary) • Change from baseline in AQLQ (S) + 12 • Change from baseline in ACQ-6
To explore change from baseline of biomarkers that may be associated with up-regulation of IL-13, and possible correlation with clinical efficacy of tralokinumab	Biomarkers will include: <ul style="list-style-type: none"> • Blood eosinophils • FENO • IgE Other biomarkers may be considered.
[REDACTED]	[REDACTED] <ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]
[REDACTED]	[REDACTED]

Results from the exploratory analyses, if performed, may be reported separately from the Clinical Study Report (CSR).

1.2 Study design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 300 mg dose of tralokinumab administered

subcutaneously in subjects with uncontrolled asthma on inhaled corticosteroids (ICS) plus long-acting β_2 -agonist (LABA), and having a history of asthma exacerbations.

Approximately 770 subjects will be randomised. Subjects will be stratified at randomisation by serum periostin (<16.44 or ≥ 16.44 ng/mL, sampled during run-in), geographical region (Asia Pacific, North America, South America/Mexico, Central/Eastern Europe, Western Europe/Rest of the World), and age group [adults (18-75 years inclusive) versus adolescents (12-17 years inclusive), defined by age at Visit 1]. Approximately 50% of the subjects are expected to be above the periostin level (≥ 16.44 ng/mL) used for stratification.

Subjects will receive either tralokinumab 300 mg, or placebo every 2 weeks administered via subcutaneous injection at the study site, over a 52-week treatment period.

In Japan, additional subjects were enrolled into the study after the global recruitment closed to allow additional Japanese subjects to be recruited. The treatment period for these additional patients will be 34 to 52 weeks depending when the subject is randomised in the study.

After initial enrolment and confirmation of entry criteria, subjects will enter a run-in period of 4 to 6 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet eligibility criteria will be randomised to a 52-week treatment period (34-week to 52-week treatment period in Japan). The first dose of tralokinumab/placebo will be administered at Week 0 (this is considered to be Day 1, for the purpose of analysis). Subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment/end of study (EOT/EOS) visit occurring at Week 52. In Japan, the last dose will be administered at any point between week 32 and 50, with end of treatment/end of study (EOT/EOS) visit occurring between week 34 and week 52, depending when the subject is randomised into the study. Subjects will be maintained on their currently prescribed ICS/LABA, without change, from enrolment throughout the run-in and treatment period. All subjects will have site visits every 2 weeks.

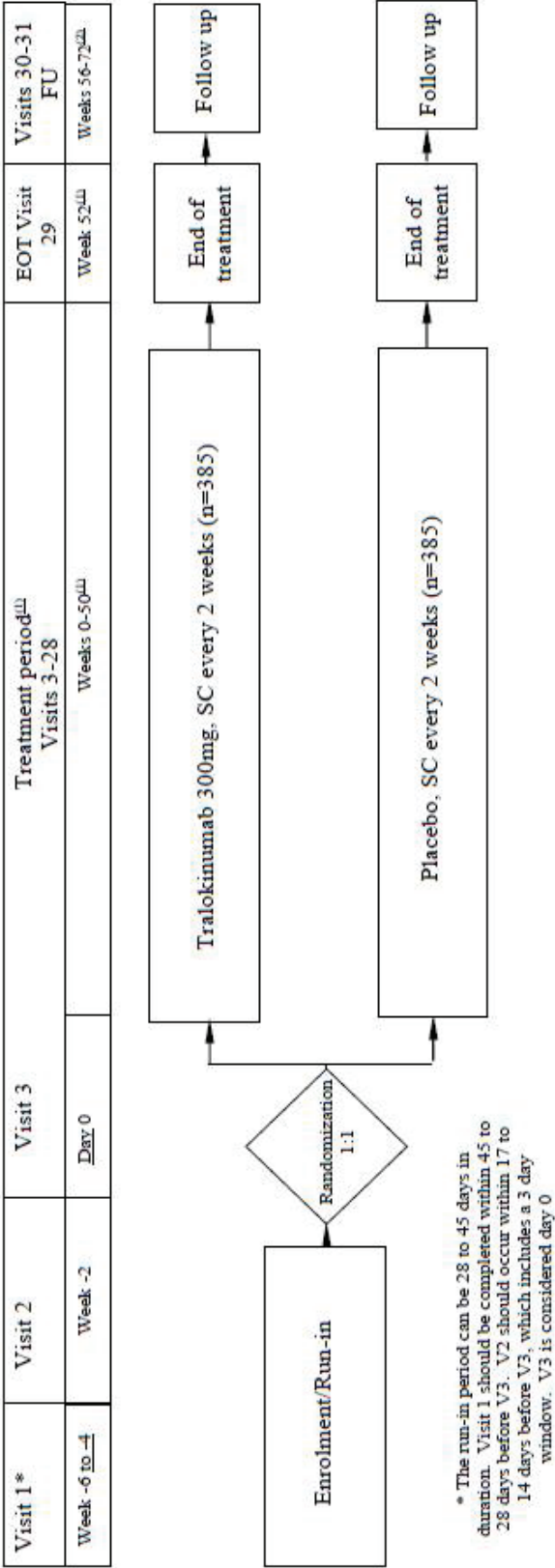
Should the subject need to discontinue investigational product (IP) for any reason, every effort should be taken for the subject to be followed-up according to one of three options:

1. Ideally the subject should return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks in the study (34 to 52 weeks in Japan), or
2. The subject will be offered to be followed up on a monthly basis via telephone calls while continuing eDiary completion, until the subject completes 52 weeks (34 to 52 weeks in Japan) in the study (no further procedures will be performed) or,
3. If the subject cannot comply or does not wish to comply with the options above, the Investigator will only contact the subject at 52 weeks (34 to 52 weeks in Japan) post randomisation. No study assessments will be performed prior to this contact

The key elements to be collected at these follow up visits or telephone contacts for options 2 and 3 are AEs/SAEs, changes in concomitant medications, and asthma exacerbation information.

Follow-up visits will be conducted at Weeks 56 and 72. The follow-up period is to ensure that determination of immunogenicity can be adequately determined. In Japan, the follow-up visits will be conducted 4 weeks and 20 weeks after the treatment period. A graphical view of the study is shown in [Figure 1](#).

Figure 1 Study flow chart



(1) In Japan, the treatment period will be 34 to 52 weeks depending when the subject is randomized into the study.
(2) In Japan, the follow up visits will be performed at Week 4 and Week 20 after EOT visit.

1.3 Number of subjects

The total study sample of 770 subjects (385 subjects per group) is considered sufficient to show a reduction in AAER for tralokinumab versus placebo in the overall study population.

Sample size calculations in terms of number of subject years needed is based on an assumed annual exacerbation rate in the placebo group of 0.8, and shape parameter of 0.95 (overdispersion) in both the all-subjects and biomarker positive population. The calculations are made for a 1% significance level for all subjects and a 4% significance level for the biomarker positive population. The methodology used is described in [Keene et al 2007](#).

Assuming a uniform loss to follow-up of 15% during the study, 770 randomised subjects are expected to provide approximately 355 subject years at risk per treatment group. This is expected to provide at least 90% power for showing superiority with effects down to 37% asthma exacerbation rate reduction in the all-subjects population.

Assuming the same prevalence as in the STRATOS 1 (D2210C00007) study, if 25% of studied subjects will fulfil the biomarker positive criteria as defined in Section 2.1, using a 5% significance level for the biomarker positive population (primary population - see revised hierarchical testing strategy in [Figure 2](#)), a true asthma exacerbation rate reduction of 50% would have a power of 80% to show superiority. [Table 1](#) below show the estimated power, if the percentage of subjects included in the biomarker positive population is between 20% and 35% of subjects randomised in this study.

Table 1 Estimated power based on biomarker positive population

% subjects in the Biomarker positive population	20%	25%	30%	35%
N per treatment group	77	97	116	135
Power	70%	80%	86%	91%

2. ANALYSIS SETS

2.1 Definition of analysis sets

All subjects analysis set: This analysis set comprises all subjects screened for the study and will be used for the reporting of disposition and screening failures.

N.B, the All subjects analysis set should not be confused with the all-subjects population.

Biomarker populations: The biomarker positive population is defined as subjects in the all subject population with a baseline $FE_{NO} \geq 37$ ppb. This cut-off is defined based on results from the STRATOS 1 (D2210C00007) study. The biomarker negative population is defined as those subjects in the all subject population not meeting the definition of the biomarker positive population.

For the reporting of efficacy data, the biomarker positive and negative population will be a subset of the Full analysis set (FAS); the primary population for analysis is the biomarker positive population. For the reporting of safety data, the biomarker positive and negative population will be a subset of the Safety analysis set. Any subjects with missing FE_{NO} data which prevents determining whether they meet the definition of the biomarker positive population, will not be included in either biomarker positive or negative population. If there are more than 10% of subjects from the all subjects population excluded from the biomarker positive and negative populations, additional summaries may be provided using this subset of “unknown” biomarker status.

2.1.1 Efficacy analysis set

Full analysis set (FAS): All subjects randomised with the potential to receive 52 weeks of IP and receiving any IP will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued. For subjects who withdraw consent or assent to participate in the study all data will be included up to the date of their study withdrawal.

Two subjects were enrolled more than once in this study using different enrolment codes. Data associated with their first enrolment code will be included in the FAS. Data recorded under additional enrolment codes will be excluded from the FAS, but will be discussed in the CSR.

FAS - Biomarker positive: All subjects in the FAS with a baseline FE_{NO} \geq 37 ppb

FAS - Biomarker negative: All subjects in the FAS with a baseline FE_{NO} $<$ 37 ppb

Full analysis set-Japan (FAS-Japan): All subjects randomised (globally) and receiving any IP will be included in the FAS-Japan, irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued. For subjects who withdraw consent or assent to participate in the study all data will be included up to the date of their study withdrawal. The FAS-Japan includes all subjects included in the FAS and in addition all subjects randomised without the potential to receive the full 52 weeks of IP.

FAS-Japan - Biomarker positive: All subjects in the FAS-Japan with a baseline FE_{NO} \geq 37 ppb

FAS-Japan - Biomarker negative: All subjects in the FAS-Japan with a baseline FE_{NO} $<$ 37 ppb

2.1.2 Safety analysis set

Safety analysis set (Safety): All subjects who received any IP will be included in the safety analysis set. Subjects will be classified according to the treatment they actually received. A subject who has on one, or several occasions, received active treatment will be classified as active. All safety summaries and ADA analysis and summaries will be based on this analysis set.

Two subjects were enrolled more than once in this study using different enrolment codes. Data associated with the first enrolment code will be included in the safety analysis set. Data recorded under additional enrolment codes will be excluded from the safety analysis set, but will be discussed in the CSR.

Any deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

Safety - Biomarker positive: All subjects in the Safety analysis set with a baseline $FE_{NO} \geq 37$ ppb

Safety - Biomarker negative: All subjects in the Safety analysis set with a baseline $FE_{NO} < 37$ ppb

2.1.3 PK analysis set

PK analysis set: All subjects in the FAS who received tralokinumab and who had blood samples obtained for PK, including PK blood samples that are assumed not to be affected by factors such as protocol deviations (e.g., disallowed medication, or incorrect study medication received) will be included in the analysis set. All PK summaries will be based on this analysis set.

PK - Biomarker positive: All subjects in the PK analysis set with a baseline $FE_{NO} \geq 37$ ppb

PK - Biomarker negative: All subjects in the PK analysis set with a baseline $FE_{NO} < 37$ ppb

2.1.4 PRO analysis set

PRO outcome variables will be evaluated based on the FAS.

All efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS. Safety objectives will be analysed based on the Safety analysis set.

2.2 Violations and deviations

Only important protocol deviations will be listed and tabulated in the CSR for all randomised subjects. These are protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being include:

- Subjects who do not meet the inclusion criteria
- Subjects who do not meet the randomisation criteria
- Subjects who meet any of the exclusion criteria
- Subjects who use one or more disallowed medication (listed in [Table 2](#) -for any reason, unless otherwise specified) during the randomised treatment period.

Table 2 Disallowed medications considered to be important protocol deviations

Medication Details	Anatomical Therapeutic Chemical (ATC) code(s)	Preferred term ^a (if applicable)
Live Attenuated Vaccines ^b	J07BD , J07BF, J07BJ, J07BK, V04CF, J07AP, J06BB, J07BB J07BH J07BL	
Any immunomodulators or immunosuppressives	L04AX, L04AD, L01BA , L04AX	
Any marketed or investigational biologic treatment	R03DX, L04AC	OMALIZUMAB MEPOLIZUMAB RESLIZUMAB
Roflumilast (Daxas/ Daliresp)	R03DX	ROFLUMILAST
Oral or ophthalmic β - adrenergic antagonist ^b	S01ED, C07AA, C07AG	
Systemic corticosteroids ^c	H02AB	

^a Preferred term will be used in combination with the ATC codes to identify medications

^b Additional physician's review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes.

^c Additional physicians review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes and duration. Only medications with a duration of ≥ 30 days will be flagged for review. Temporary use (< 30 days) of systemic corticosteroids for treatment of asthma exacerbations or other acute conditions is allowed.

- Subjects who received the incorrect study treatment or study dose at any time during the 52-week (34-week to 52-week in Japan) double-blind treatment period
- Subjects who developed withdrawal/discontinuation of IP criteria during the study but were not withdrawn/discontinued from IP.
- Subjects reporting any Good Clinical Practice (GCP) deviations

All important protocol deviations will be identified and documented by the AZ study physician and statisticians prior to unblinding of the data.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General Definitions

3.1.1 Definition of baseline

In general, the last measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints, while the last measurement prior to first dose of study treatment will serve as the baseline measurement for safety endpoints.

For spirometry variables (FEV₁, FVC and FEF_{25-75%}) the measurement recorded at the baseline visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing, the last non-missing value before Visit 3 will be used as baseline instead. For post-BD measurements,

where it is possible to have multiple spirometry records, per time point, the first measurement will be used (i.e. the measurement after the first BD administration); for reversibility, this will be the first measurement when the reversibility assessment was considered complete (see Section 3.1.4).

For FE_{NO}, the measurement recorded at the baseline visit (Visit 3) will be used as baseline. If the Visit 3 measurement is missing, the last non-missing value before Visit 3 will be used as baseline instead.

The baseline for ePRO variables (ACQ-6, AQLQ(S) +12, WPAI-CIQ, and EQ-5D-5L) will be captured or derived from what is captured on the ePRO device at Visit 3. Baseline for Asthma Daily Diary variables will be the bi-weekly mean for data collected between the evening of day -14 and the morning of day 1, where day 1 is the day of randomisation. . If more than 7 daily scores (>50%) within that period is missing, the baseline will be set to missing.

For analysis of bi-weekly means for Asthma Daily Diary variables where ‘at Week 52’ is referred to, this should be interpreted as ‘at Period 26’, as defined in Section 3.3.

For laboratory data, vital signs, and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose. If no time is recorded for an assessment, and the assessment takes place at Visit 3, this will be assumed to be a pre-dose assessment.

For dECG, the measurement recorded at Visit 1 will be used as baseline.

3.1.2 FE_{NO}

[illegible]

1. *Journal of Management Studies*, 1996, 33, 1, 1-15.

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.1.3 Absolute and percent change from baseline

Absolute change from baseline outcome variables is computed as

$$(post-randomisation\ value - baseline\ value).$$

Percent change from baseline is computed as

$$((post-randomisation\ value - baseline\ value) / baseline\ value) \times 100\%.$$

If either the post-randomisation value or the baseline value is missing, then the absolute or percent change from baseline value will also be set to missing.

3.1.4 Reversibility

Reversibility percentage will be computed as

$$\% \text{ Reversibility} = (post-BD\ FEV_1 - pre-BD\ FEV_1) \times 100 / pre-BD\ FEV_1$$

The FEV₁ post-BD measurement in the reversibility derivation will be the latest measurement and can be the post-BD measurement after 4, 6 or 8 SABA inhalations, depending on when the reversibility assessment was considered complete.

3.1.5 Visit and period windows

For the exacerbation-related analyses no windows will be applied.

For local laboratory data, vital signs, physical examination, and ADA, the visit recorded in the Web Based Data Capture system will be used.

For the central laboratory results, spirometry, AQLQ(S) +12, ACQ-6, and WPAI+CIQ, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit

windows as defined in [Table 3](#). EQ-5D-5L will be summarised using the windows as defined in [Appendix A, Table 7](#).

Any data collected at unscheduled visits will be listed, included within baseline data in shift plots and reversibility summaries, and will be included in the definition of maximum /minimum within-period value, but will not be included in summaries by visit. In case of a missing assessment at a scheduled visit followed by an unscheduled visit, the unscheduled assessment will not replace the missing result in the summary outputs by period and visit.

If appropriate, i.e. if a substantial percentage of observations for a variable fall outside the adjusted window, sensitivity analysis will be performed where observations are assigned accor

Table 3 Visit windows

Visit	Target Day	Adjusted analysis-defined Visit windows:	Extended windows for sensitivity analyses:			
			Haematology, AQLQ(S)+12	Pre BD Spirometry	Post BD Spirometry	Clinical chemistry, Urinalysis
Baseline (Week 0) ^a	1	1	1	1	1	1
Week 2	15	2-21	2-21 ^b	2-21	-	-
Week 4	29	22-35	22-42 ^b	22-35	-	2-42
Week 6	43	36-49	-	36-49	-	-
Week 8	57	50-63	43-70	50-70	2-210	43-119
Week 10	71	64-77	-	-	-	-
Week 12	85	78-91	71-98	71-98	-	-
Week 14	99	92-105	-	-	-	-
Week 16	113	106-119	99-126	99-147	-	-
Week 18	127	120-133	-	-	-	-
Week 20	141	134-147	127-154	-	-	-
Week 22	155	148-161	-	-	-	-
Week 24	169	162-175	155-182	-	-	-
Week 26	183	176-189	-	148-203	-	120-231
Week 28	197	190-203	183-210	-	-	-
Week 30	211	204-217	-	-	-	-
Week 32	225	218-231	211-238	204-252	-	-
Week 34	239	232-245	-	-	-	-
Week 36	253	246-259	239-266	-	-	-
Week 38	267	260-273	-	-	-	-
Week 40	281	274-287	267-294	253-322	-	232-322
Week 42	295	288-301	-	-	-	-

Table 3 Visit windows

Visit	Target Day	Adjusted analysis-defined Visit windows:	Extended windows for sensitivity analyses:			
			Haematology, AQLQ(S)+12	Pre BD Spirometry	Post BD Spirometry	Clinical chemistry, Urinalysis
Week 44	309	302-315	295-322	-	-	-
Week 46	323	316-329	-	-	-	-
Week 48	337	330-343	323-350	-	-	-
Week 50	351	344-357	-	-	-	-
Week 52	365	358-378	351-378	323-378	211-378	323-378
Week 56 (FU)	393 ^d	379-448 ^d	379-448 ^c	-	-	-
Week 72 (FU)	505 ^e	449-560 ^e	449-560 ^c	379-560	-	-

^a If the Day 1 assessment is missing, see Section 3.1.1 on how baseline value is defined.

^b Week 2 is not applicable for AQLQ(S)+12. Week 4 visit window for AQLQ(S)+12 will be 2-42.

^c Not applicable for AQLQ(S)+12.

^d In Japan, the FU target day will be EOT target day +16; visit windows are FU target date-14 to FU target day+55.

^e In Japan, the FU target day will be EOT target day +140; visit windows are FU target date-55 to FU target day+55.

For assignment of data to time points using the visit windows, study day will be defined as follows for efficacy endpoints:

$$(\text{Date of assessment} - \text{Date of randomisation}) + 1.$$

And as follows for safety endpoints:

$$(\text{Date of assessment} - \text{Date of first dose of IP}) + 1.$$

In case of multiple observations within a single visit window, the following rules apply:

- If there are two or more observations within the same visit window, the non-missing observation closest to the target day will be used in the analysis
- If two observations are the same distance away from the target day, the non-missing observation with the earlier collection date will be used in the analysis
- If two observations are collected on the same day and have a collection time associated with them, the non-missing observation with the earlier collection time will be used in the analysis
- If two or more observations are collected on the same day, all non-missing but with no collection time associated with at least one of them, the average of the observations will be used in the analysis.

If a visit window does not contain any observation, then the data will be missing for that visit.

3.2 Calculation or derivation of efficacy variables

3.2.1 Exacerbation rate

The primary endpoint is the AAER up to Week 52. For the primary analysis the response variable is the number of exacerbations the subject experiences up to Week 52, with the time at risk of experiencing an exacerbation included as offset in the model.

An asthma exacerbation is defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- An ER or UC visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma

In order to calculate the number of exacerbations experienced by a subject during the 52-week treatment period (34-week to 52-week in Japan) the following rules will be applied:

- The start of an exacerbation is defined as the start date of systemic corticosteroids, ER or UC visits requiring systemic corticosteroids, or hospital admissions due to asthma, whichever occurs earlier,
- The end date is defined as the last day of systemic corticosteroids or ER/UC/hospital discharge, whichever occurs later.

Two or more exacerbations with the same start date and end date will be counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a subject. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these will be counted as one exacerbation, using the earliest exacerbation start date and the latest exacerbation stop date to calculate duration.

Additional systemic corticosteroid treatments, ER or UC visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation will not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. If two or more exacerbations are recorded less than 7 days apart, these will be counted as one exacerbation, but the duration period of each exacerbation will be considered separately when calculating exacerbation duration for subject.

Maximum follow-up time for a subject is approximately 52 weeks (34 to 52 weeks in Japan); defined as the time from randomisation to the date of EOT visit. For a subject lost to follow-

up, this will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed, (i.e., the last contact date). Any exacerbations after this time point will not be included in analyses.

For the primary analysis, exacerbations that occur after a subject has discontinued IP but before maximum follow-up time will still be accounted for when deriving the total number of exacerbations. Likewise, the follow-up time will reflect the follow-up time regardless of whether or not the subject is still on IP.

For the production of summary statistics, the annual exacerbation rate per subject is calculated and standardized per a 52-week period according to the formula described below.

*Annual Exacerbation Rate = No. of Exacerbations * 365.25 / time at risk of experiencing an exacerbation.*

Where time at risk of experiencing an exacerbation is defined as follow-up time (follow-up date - date of randomisation + 1) minus the number of days the subject experiences a protocol defined exacerbation including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation).

3.2.2 Proportion of subjects with ≥ 1 asthma exacerbation during 52 weeks of treatment

The proportion of subjects with ≥ 1 asthma exacerbation during the 52 weeks of treatment will be a supportive measurement to the primary objective. The outcome variable will categorize each subject as having at least one asthma exacerbation or not (yes=1/no=0).

The proportion of such subjects will be calculated for each treatment group as:

Number of subjects with ≥ 1 asthma exacerbation during the 52 week treatment period / number of subjects in treatment group

3.2.3 Time to first exacerbation

Time from randomisation to the first asthma exacerbation will also be used as a supportive variable to the primary objective, and is calculated as follows:

Start Date of first asthma exacerbation - Date of Randomisation + 1.

The time to first asthma exacerbation for subjects who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 52-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up subjects).

3.2.4 Annual rate of asthma exacerbations that are associated with an ER or UC visit or a hospitalisation

The AAER associated with an ER or UC visit or a hospitalisation (as a subset of the primary variable defined in Section 3.2.1), will be a secondary efficacy variable.

The number of asthma exacerbations that are associated with an ER or UC visit or a hospitalisation experienced by a subject during the 52-week treatment period will be derived using the same rule for start and end as described for the primary variable in Section 3.2.1.

Maximum follow-up time is approximately 52 weeks, and the follow-up time is derived as (Follow-up date - Date of randomisation + 1) minus the number of days the subject experiences a protocol defined exacerbation associated with an ER or UC visit or a hospitalisation including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation).

Additionally, for the production of descriptive statistics, the annualised rate of asthma-related ER or UC visits and hospitalisations will be calculated and standardized per a 52-week period according to the formula described below.

*Annual Exacerbation Rate = No. of Exacerbations associated with an ER or UC visit or a hospitalisation *365.25 / time at risk of experiencing an exacerbation.*

Where time at risk of experiencing an exacerbation is defined follow-up time minus the number of days the subject experiences a protocol defined exacerbation associated with an ER or UC visit or a hospitalisation including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation).

3.2.5 Forced expiratory volume in 1 second

The key secondary variable is the pre-dose/pre-BD FEV₁ which will be determined by spirometry. To ensure quality control all spirometries are reviewed to ensure that they meet ATS/ERS criteria for acceptability. Only those spirometry tracings determined to be acceptable or borderline will be used to determine FEV₁ (and FVC and FEF_{25-75%}), based on the best measurement selected by ERT per spirogram. Section 5.1.2 of the CSP contains further details of the spirometry recordings.

The percent change from baseline to each of the post-randomisation visits, up to and including the end of 52-week double-blind treatment visit (Visit 29), will be used as secondary efficacy outcome variable.

The absolute change from baseline to each of the post-randomisation visits up to and including the end of 52-week double-blind treatment visit (Visit 29) will be used as a supportive variable.

The same outcome variables will be derived for the secondary variable pre-dose/post-BD FEV₁.

3.2.6 Forced Vital Capacity and Forced Expiratory Flow at 25-75%

The percent change from baseline to each of the post-randomization visits, up to and including the end of 52-week double-blind treatment visit (Visit 29) will be calculated for the exploratory variables FVC and FEF_{25-75%}.

3.3 Calculation or derivation of patient reported outcome variables

Patient-reported outcomes data will be captured via an ePRO device. The definition of key secondary and secondary outcome variables based on the ePRO is provided in the following sections. For all outcomes based on the ePRO devices, analyses will be based on data up to and including week 52.

For asthma symptom score, rescue medication use, and home peak expiratory flow, bi-weekly means will be calculated. A bi-weekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential rolling days divided by the number of non-missing daily measures/scores. For nights with awakenings due to asthma, the bi-weekly mean will be the percentage of times the subject answered “yes” to ‘did your asthma cause you to wake up’ and “yes” to ‘did you use rescue medication upon awakening’. If more than 7 daily measures/scores (>50%) within a period is missing, then the bi-weekly mean for that period is set to ‘missing’. Note that the first bi-weekly mean in the treatment period will be based on the evening recording on day 1 up to and including the morning recording on day 15. The daytime score is recorded in the evening and the night-time score is recorded the following morning.

Bi-weekly periods are defined as follows (where Day 1 is the day of randomisation)

Bi-weekly Period	Label
Baseline (as defined in Section 3.1.1)	(Day -14 to 1) Baseline
Period 1: Evening of Day 1 - Morning of Day 15	Day 1 - 15 (Week 2)
Period 2: Evening of Day 15 - Morning of Day 29	Day 15 - 29 (Week 4)
Period 3: Evening of Day 29 - Morning of Day 43	Day 29 - 43 (Week 6)
Period 4: Evening of Day 43 - Morning of Day 57	Day 43 - 57 (Week 8)
Period 5: Evening of Day 57 - Morning of Day 71	Day 57 - 71 (Week 10)
Period 6: Evening of Day 71 - Morning of Day 85	Day 71 - 85 (Week 12)
Period 7: Evening of Day 85 - Morning of Day 99	Day 85 - 99 (Week 14)
Period 8: Evening of Day 99 - Morning of Day 113	Day 99 - 113 (Week 16)
Period 9: Evening of Day 113 - Morning of Day 127	Day 113 - 127 (Week 18)
Period 10: Evening of Day 127 - Morning of Day 141	Day 127 - 141 (Week 20)
Period 11: Evening of Day 141 - Morning of Day 155	Day 141 - 155 (Week 22)
Period 12: Evening of Day 155 - Morning of Day 169	Day 155 - 169 (Week 24)
Period 13: Evening of Day 169 - Morning of Day 183	Day 169 - 183 (Week 26)
Period 14: Evening of Day 183 - Morning of Day 197	Day 183 - 197 (Week 28)
Period 15: Evening of Day 197 - Morning of Day 211	Day 197 - 211 (Week 30)
Period 16: Evening of Day 211 - Morning of Day 225	Day 211 - 225 (Week 32)
Period 17: Evening of Day 225 - Morning of Day 239	Day 225 - 239 (Week 34)
Period 18: Evening of Day 239 - Morning of Day 253	Day 239 - 253 (Week 36)
Period 19: Evening of Day 253 - Morning of Day 267	Day 253 - 267 (Week 38)

Bi-weekly Period	Label
Period 20: Evening of Day 267 - Morning of Day 281	Day 267 - 281 (Week 40)
Period 21: Evening of Day 281 - Morning of Day 295	Day 281 - 295 (Week 42)
Period 22: Evening of Day 295 - Morning of Day 309	Day 295 - 309 (Week 44)
Period 23: Evening of Day 309 - Morning of Day 323	Day 309 - 323 (Week 46)
Period 24: Evening of Day 323 - Morning of Day 337	Day 323 - 337 (Week 48)
Period 25: Evening of Day 337 - Morning of Day 351	Day 337 - 351 (Week 50)
Period 26: Evening of Day 351 - Morning of Day 365	Day 351 - 365 (Week 52)

Where a total score is calculated for a day (e.g. Asthma symptom score), this calculation will spans two calendar days - the daytime value recorded in evening of day X, and the night time value recorded on morning of day x+1. E.g. the Asthma Symptom score on Day 1 will be the day time score recorded on the evening of Day 1 + the night-time score recorded on the morning of Day 2

Where only night-time scores/results are of interest, the morning entries on the second day of a period up to and including the morning entry on the last day of the period (or morning of the last day of study for the last period/last IP intake) will be considered.

Where only daytime scores/results are of interest, the evening entries on the first day of the period up to and including the evening entry on the second last day of the period (or evening before the last day of study/last IP intake) will be considered.

3.3.1 Asthma symptom score

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning), and total score will be calculated separately.

The daily asthma symptom total score will be calculated by taking the sum of the daytime score recorded in the evening and the nighttime score recorded the following morning (Section 3.3). If a subject is missing a value for either night-time or daytime asthma symptom score on a given day then the total score for that day will be set to missing.

The key secondary outcome variable is the change from baseline in bi-weekly mean daily asthma symptom total score. Bi-weekly means and change from baseline for daytime and night-time scores will also be calculated.

The number of asthma symptom-free days will be calculated for each patient as the total number of days in the 52 week treatment period where the total asthma symptom score is 0. The proportion of asthma symptom-free days will be calculated using the total number of days

with completed asthma symptom score diary during the 52 week treatment period as the denominator.

3.3.2 Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning. Inhaler usage will be reported as the number of puffs in a given period whereas nebulizer use will be reported as the number of times.

The number of inhalations of rescue medication and nebulizer treatments captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either night-time or daytime rescue medication on a given day, then the total rescue medication use for that day will be set to missing.

The number of inhalations (puffs) per day will be calculated as follows:

Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times].

Bi-weekly mean change from baseline in the number of inhalations (puffs) per day will be calculated as the outcome variable.

3.3.3 Nights with awakening due to asthma

Bi-weekly mean change from baseline in the number (percentage) of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable.

3.3.4 Home peak expiratory flow (morning and evening)

Bi-weekly mean absolute changes from baseline in morning and evening PEF will be calculated.

3.3.5 Asthma Control Questionnaire (ACQ-6)

In the ACQ-6 questionnaire the subjects are asked to recall the status of their asthma during the previous week with regards to symptom and use of short acting β -agonists. Subjects will be asked to complete ACQ-6 once every 2 weeks. The questionnaire include questions on

1. Awoken at night by symptoms
2. Limitation of normal daily activities
3. Waking in the morning with symptoms
4. Dyspnoea
5. Wheeze
6. Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the un-weighted mean of the responses to the 6 questions. If response to any of the questions is missing, the ACQ-6 will be missing.

The key outcome variable for the ACQ-6 will be the change in mean score from baseline to each of the post-randomisation assessments. The change from baseline for each question will also be calculated.

Other variables based on ACQ-6 to report include:

- ACQ-6-responder (Yes=1/No=0)
 - Responder: Change from baseline ACQ-6 score ≤ -0.5
 - Non-responder : Change from baseline ACQ-6 score > -0.5
- ACQ-6-responder (Improved/No Change / Deterioration)
 - Improvement: Change from baseline ACQ-6 score ≤ -0.5
 - No change: $-0.5 < \text{Change from baseline ACQ-6 score} < 0.5$
 - Deterioration: Change from baseline ACQ-6 score ≥ 0.5
- Subjects asthma control as measured by ACQ-6 score:
 - Well controlled : ACQ-6 score ≤ 0.75
 - Partly controlled : $0.75 < \text{ACQ-6 score} < 1.5$
 - Not well controlled : ACQ-6 score ≥ 1.5

Subjects with missing or non-evaluable ACQ-6 score at week 52 will be considered as a non-responder for ACQ-6 responder (Yes=1/No=0).

3.3.6 Asthma quality of life questionnaire for 12 years and older (AQLQ(S) +12)

In the AQLQ(S)+12 the subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). Subjects will be asked to complete AQLQ(S) +12 once every 4 weeks.

The overall score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains. The following are the question numbers on the AQLQ(S) +12 questionnaire relating to each domain:

Table 4 AQLQ(S) +12 Domains

Domain	AQLQ(S)+12 question numbers
Symptoms	6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitations	1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function	7, 13, 15, 21, 27
Environmental Stimuli	9, 17, 23, 26

If response to any of the questions is missing the overall score will be missing, if response to a question within a domain is missing, the score for that domain will be missing.

The key outcome variable for the AQLQ(S) +12 will be the change in overall score from baseline to each of the post-randomisation assessments. Change from baseline in each domain will also be calculated.

Other variables based on AQLQ(S) +12 to be reported include:

- AQLQ(S) +12 -responder (Yes=1/No=0)
 - Responder: Change from baseline AQLQ(S) +12 score ≥ 0.5
 - Non-responder : Change from baseline AQLQ(S) +12 score < 0.5
- AQLQ(S) +12 -responder (Improved/No Change/Deterioration)
 - Improvement: Change from baseline AQLQ(S) +12 score ≥ 0.5
 - No change: $-0.5 < \text{Change from baseline AQLQ(S) +12 score} < 0.5$
 - Deterioration: Change from baseline AQLQ(S) +12 score ≤ -0.5

Subjects with missing or non-evaluable AQLQ(S) +12 score at week 52 will be considered as a non-responder for AQLQ(S) +12 -responder (Yes=1/No=0).

3.3.7 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale (VAS), where the subject will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The change from baseline in VAS will be calculated by assessment.

3.3.8 Health care resource utilization

Health care resource utilization due to asthma will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the HEVENT module in the eCRF.

Study period number of days/times will be calculated for each subject for the following variables:

- Ambulance transport
- Hospitalisation (number of visits and days in hospital)
 - Intensive care (days in intensive care)
 - General care (days in general care)
- ER visit
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician
- Home visit, other health care
- Telephone call, physician
- Telephone call, nurse
- Spirometry
- Advanced pulmonary function test

The study period number per subject will be determined as:

Study period number = Sum of 'total No. of times/days' as entered in HEVENT up to Week 52.

3.3.9 The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ questionnaire is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. Subjects will be asked to complete WPAI+CIQ once every 2 weeks.

There are a maximum of 10 questions and a minimum of 3 questions that will be completed by subjects as follows:

1. Currently employed (yes/no)
2. Hours missed work due to health problems
3. Hours missed work due to other reasons
4. Hours actually worked
5. Degree health affected productivity while working (0-10 scale, with 0 meaning no effect)
6. Attends class in an academic setting (yes/no)

7. Hours missed class due to health problems
8. Hours actually attended class
9. Degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)
10. Degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 is 'No, not currently employed', then the subject should skip to question 6. If the answer to question 6 is 'No, not currently attending class', then the subject should skip to question 10.

The WPAI+CIQ provide 4 scores:

- Absenteeism (work or class time missed),
- Presenteeism (impairment at work or class/reduced on-the-job effectiveness),
- Work productivity loss (overall work or class impairment/absenteeism plus presenteeism)
- Activity impairment.

WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For each time point at which the WPAI-CIQ is administered, the following descriptive statistics (if applicable) (n, total number of hours, mean per subject, standard deviation (SD), median, minimum and maximum) will be reported for those who are employed:

- # employed
- % of all subjects employed
- # of work hours missed due to asthma
- Absenteeism due to asthma
- Presenteeism due to asthma
- Work Productivity Loss
- Activity impairment

The following formulas will be used to calculate each of the outcome measures listed above:

- # currently employed - Yes in response to Question 1
- # of hours missed due to asthma - as responded in Question 2
- Absenteeism = $Q2/(Q2+Q4)$

- Presenteeism = $Q5/10$
- Work Productivity Loss = $Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]$
- Activity Impairment = $Q10/10$

Similarly, the following will be reported for those subjects who are in school:

- # in school
- % of all subjects in school
- # of class hours missed
- Absenteeism due to asthma
- Presenteeism due to asthma
- Class Productivity Loss
- Activity impairment

The following formulas will be used to calculate each of the outcomes measures listed above:

- # in school - Yes to Question 6
- # of class hours missed due to asthma - as responded on Question 7
- Absenteeism due to asthma - $Q7/(Q7+Q8)$
- Presenteeism due to asthma - $Q9/10$
- Class Productivity Loss - $Q7/(Q7+Q8) + [(1-Q7/(Q7+Q8))x(Q9/10)]$
- Activity Impairment = $Q10/10$

In addition, activity impairment will be presented for those who are not employed, not in school, and all subjects.

3.3.10 Clinical global impression of change (CGIC)

CGIC is used for an overall evaluation of response to treatment. The Investigator (clinician) uses a 7-point scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse.

The Investigator will be asked to rate the degree of change in the overall asthma status compared to the baseline visit. The CGIC assessment was added through a protocol amendment, therefore not all subjects in the FAS will have these assessments. Calculation of percentages will be based on the number of subjects in the FAS set with a completed assessment. There will be no imputation for missing values.

Subjects will also be categorized as Improved, Much Improved and Very Much Improved according to the following responses post-baseline:

- Improved: subjects in this category will include those with responses of ‘Very much improved’, ‘much improved’ and ‘minimally improved’.
- Much Improved: subjects in this category will include those with responses of ‘Very much improved’, ‘much improved’.
- Very Much Improved: subjects in this category will include those with responses of ‘Very much improved’.

Subjects can be counted in more than one category at a given time point.

3.4 Calculation or derivation of safety variable(s)

The following safety data will be collected: vital signs, physical examination, 12-lead dECG, haematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (Visit 3) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements.

3.4.1 Adverse events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

AE data will be categorized according to their onset date into the following periods:

- AEs occurring during run-in (onset date \geq Visit 1 and before the first dose of IP)
- AEs occurring during study (onset date \geq the first day of IP and \leq Visit 31 (Week 72))
- AEs occurring during treatment (onset date \geq the first day of IP and \leq the last day of IP + 2 weeks)
- AEs occurring post-treatment (onset date $>$ the last day of IP + 2 weeks and \leq Visit 31 (Week 72))

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on treatment AE. The same during treatment definition will be used for laboratory and physical examination data, where applicable.

3.4.2 Safety topics of special attention

Although the CSP did not describe AEs of special interest, AstraZeneca Patient Safety and study physicians review all AEs and identify those that merit special attention. These AEs fall into three categories, AEs possibly related to administration of biologics (e.g., anaphylaxis/hypersensitivity reactions and injection site reactions), AEs possibly related to the mechanism of action of tralokinumab as an IL-13 blocking agent (e.g., infections such as severe, viral, invasive fungal, and parasitic, malignancy, cardiovascular/cerebrovascular events, pregnancy/spontaneous abortion and increased eosinophils) and AEs reported for other biologics in this class (e.g., musculoskeletal). AEs falling into the category of safety topics of special attention will be tabulated.

3.4.3 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP. Blood samples for determination of haematology/haemostasis and clinical chemistry will be performed at a central laboratory. Urine samples will be analysed locally and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed. The parameters outlined in Table 2, Table 3, Table 4 and Table 5 in Section 5.1.6.1 of the CSP and Glycosylated haemoglobin (HbA1c) will be collected. Laboratory data will be reported in SI units.

Changes in haematology (including HbA1c) and clinical chemistry variables between baseline and each subsequent on treatment scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), trace, or positive (+) at each time-point.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and on-treatment will be defined as the latest non-missing assessment, using the ‘during treatment’ definition as defined in Section 3.4.1

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), S-Gamma-glutamyl transpeptidase (GGT) and total bilirubin (TBL), the multiple of the AstraZeneca upper limit of the normal (ULN) (not extended) range will be calculated for each data point.

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

- $\text{AST} \geq 3 \times \text{ULN}$

- ALT $\geq 3x$ ULN
- TBL $\geq 2x$ ULN

3.4.4 dECGs

Twelve-lead dECG measurements will be recorded in accordance with the protocol.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in Table 1 in the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.1.7 of the CSP. For the brief physical examination, only information on whether the assessment was performed or not will be recorded.

Each component of the Visit 1 complete physical examination will be recorded as normal or abnormal. Each component of the complete physical examinations from Visit 3 onwards will be recorded as normal, same as Visit 1, or new/aggravated.

Any new finding(s), or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.4.6 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature) will be obtained in accordance with the schedule provided in Table 1 in the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range in [Table 5](#) and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Table 5 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change Criteria
Diastolic Blood Pressure (sitting)	mmHg	<60	>100	± 15
Systolic Blood Pressure (sitting)	mmHg	<90	>160	± 30
Pulse (sitting)	Beats/min	<50	>100	± 20
Respiratory Rate	Breaths/Min	<8	>20	
Body Temperature	Celsius	<36	>37.5	
Weight	kg	<40	>150	

Body mass index (BMI) will be calculated from the height (in meters) and weight (in kilograms) as follows:

$$BMI = kg/m^2$$

3.4.7 Medical History

The principal for imputing incomplete diagnosis dates when calculating the number of years since diagnosis (earliest possible date) is shown in [Table 6](#) below:

Table 6 Approach to incomplete diagnosis dates for medical history

Date of Birth (Year-Month-Day)	Diagnosis Date (Year-Month-Day)	Date for use in calculations (Year-Month-Day)
1951-09-16	1951-10-10	1951-10-10
1951-09-16	1951-10-UK	1951-10-01
1951-09-16	1951-UK-UK	1951-10-16
1951-09-16	1952-UK-UK	1952-01-01

UK = Unknown

3.4.8 Calculations or derivation of Pharmacokinetic and Immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects at baseline prior to first IP administration at Visit 3, at multiple time points before IP administrations during the treatment period, and at selected time points in the follow-up period of the study. Anti-drug antibody (ADA) assessments will be conducted utilizing a tiered approach (screen, confirm, titre). These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titre values are reported as the reciprocal of the highest dilution that yields a value above the cut point. Samples from pre-defined study time points that confirm positive for ADA will also be tested for neutralizing ADA (nAb) activity. Both ADA and nAb will be summarised using descriptive statistics as described in [Section 4.2.7.7](#).

Pharmacokinetics and immunogenicity of tralokinumab:

Tralokinumab serum concentrations will be tabulated by time along with descriptive statistics. Population PK modelling may also be performed to better characterize the PK of tralokinumab, but will be reported separately from the CSR.

If possible, and if relevant, the impact of ADA occurrence on the PK and PD and safety will be summarised in the CSR. Summaries of tralokinumab serum concentrations by time will be summarised by ADA status (positive vs negative).

4. ANALYSIS METHODS

4.1 General principles

The main focus for the statistical analyses is to compare tralokinumab to placebo in the biomarker positive population, with regards to primary, key secondary, and safety objectives. In addition when the biomarker positive population is reported the complement population, the biomarker negative population, will also be reported.

The analysis of the study endpoints will include all data captured during the 52-week double-blind treatment period. This includes data regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the subject withdraws consent or assent to study participation.

Only exacerbations that can be determined to be protocol defined exacerbations (CSP Section 5.1.1) will be included in efficacy analysis and summaries. This includes only exacerbations that started on or after the date of randomisation, and those that are defined as a worsening of asthma that leads in at least one of the three criteria detailed in Section 3.2.1 being fulfilled. From the EXACA form on the eCRF, for a given exacerbation this will include exacerbations where EXACDRY= 'Yes' and at least one of the following a) EXSCORT = 'Yes' b) EXSCORT = 'Yes' and EXERTRT = 'Yes' c) HOSPIT = 'Yes'. Supportive analysis of exacerbations based on adjudicated data will be based on all hospitalisations or ER/UC visits determined to be related to asthma by the independent adjudication committee. Any events with an undetermined adjudication outcome will be regarded as related to asthma if the investigator has recorded the event as a protocol defined exacerbation in the eCRF, otherwise it will be assumed to be not related to asthma.

Summary data will be presented in tabular format by treatment. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarised by descriptive statistics including N, mean, SD, median, and range. All data will be listed. Data listings will be sorted by treatment and subject number.

Minimum and maximum values will be reported to the same degree of precision as the raw data unless otherwise stated. Mean, median, SD and confidence intervals (CIs) will be reported to one further degree of precision.

All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 4 decimal places.

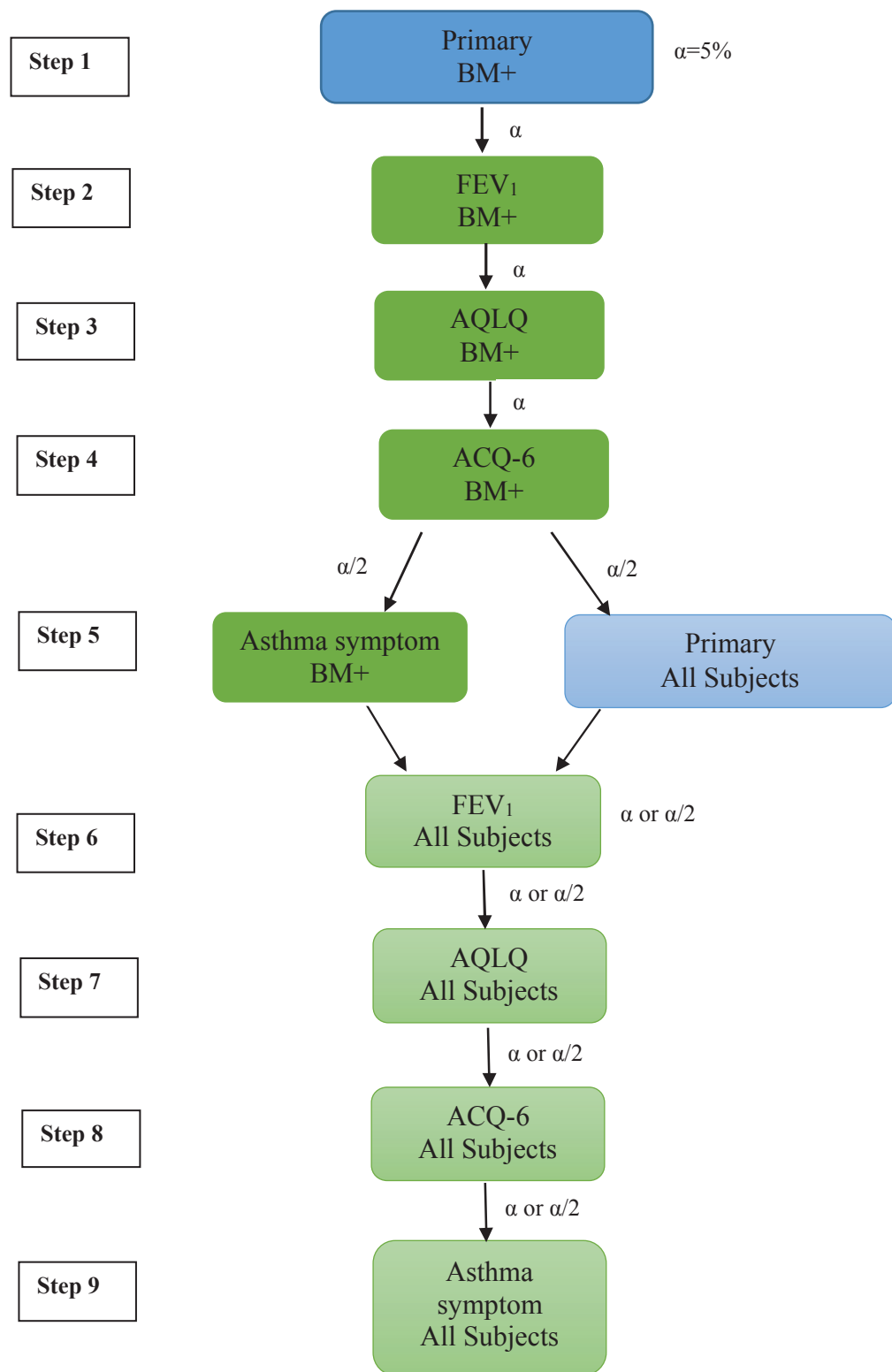
If a treatment effect is deemed sufficient for initiating interactions with PMDA, some of the analyses described in this SAP will be repeated for Japanese subjects separately to explore consistency of treatment effect between all subjects and Japanese subjects. The exploration will be primarily based on FAS for efficacy, Safety analysis set for safety, and PK analysis set for PK. Additional exploration with regards to efficacy will be conducted based on FAS-Japan. The biomarker status will be taken into account upon analysis, as appropriate. Subjects

enrolled in Japan will be considered as Japanese for these analyses. These analyses, if performed, will be reported separately from CSR.

4.1.1 Testing strategy for primary and key secondary objectives

The pre-defined hierarchical testing strategy for testing of the primary and key secondary hypothesis presented in [Figure 2](#) and further described in the text below, gives global strong control of the Type I error (FWER).

Figure 2 Hierarchical Testing strategy



Step 1: The primary endpoint in the biomarker positive population will be tested two-sided at $\alpha=0.05$

Step 2: If a significant treatment effect is shown with regards to the primary endpoint in the biomarker positive population in Step 1, then the key secondary endpoint, percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 vs. placebo will be tested two-sided at $\alpha=0.05$ within that population using the hierarchical testing approach shown in [Figure 2](#). Otherwise, testing will stop. All subsequent results within the hierarchy will be declared non-significant.

Steps 3 and 4: The testing will continue as described in steps 1 and 2, where testing will be performed two-sided at $\alpha=0.05$ within that population, only if a significant treatment effect is shown in the previous step. Testing will continue at each step until a treatment effect is not shown. At that step, testing will stop, with all subsequent results within the hierarchy declared non-significant.

Step 5: If a significant treatment effect is shown with regards to the key secondary endpoint of change from baseline in ACQ-6 at Week 52 vs placebo in the biomarker positive population, then the key secondary endpoint of change from baseline in bi-weekly mean daily asthma symptom score at Week 52 vs placebo in the biomarker positive population and the primary endpoint in the all subjects population will be tested using a Bonferroni approach at significance α . Hence, each of the two endpoints will be tested at significance level $\alpha/2$ ($=0.025$). If at least one significant treatment effect is shown at this step, testing will continue to step 6. Otherwise, testing will stop. All subsequent results within the hierarchy will be declared non-significant.

Step 6: Percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 vs. placebo in the all subjects population will only be tested if at least one significant treatment effect is shown at step 5. There are two different outcomes in Step 5 that could result in testing the hypothesis for FEV₁:

- (a) If both comparisons in step 5 exhibits significance, then FEV₁ in the all subjects population is testable and will be tested at significance level α ($=0.05$).
- (b) If only one of the hypotheses in step 5 exhibits significance, then FEV₁ in the all subjects population is testable and will be tested at significant level $\alpha/2$ ($=0.025$).

Step 7: If a significant treatment effect is shown with regards to percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 vs. placebo in the all subjects population then change from baseline in AQLQ(S)+12 at Week 52 vs placebo will be tested using the significance level used in step 6 (α ($=0.05$) if outcome (a) from Step 5, or $\alpha/2$ ($=0.025$) if outcome (b) from step 5). Otherwise, testing will stop. All subsequent results within the hierarchy will be declared non-significant.

Steps 8 and 9: The testing will continue as described in step 7, where testing will be performed two-sided at α ($=0.05$) or $\alpha/2$ ($=0.025$), only if a significant treatment effect is shown in the previous step. Testing will continue at each step until a treatment effect is not

shown. At that step, testing will stop, with all subsequent results within the hierarchy declared non-significant.


4.1.2 Sensitivity analyses

Sensitivity analyses for the primary endpoint and the key secondary continuous endpoints based on different missing data mechanism assumptions will be performed. These analyses are detailed in [Appendix B](#).

In addition to the methods described in [Appendix B](#), the following analyses will also be performed;

- The primary analysis will be repeated, in the FAS (all subject population and the biomarker positive and negative populations), where the time at risk (which is included in the model as an offset variable) does not exclude time during which a subject is having an exacerbation (see Section 4.2.4).
- The primary analysis will be analysed in the FAS biomarker positive population, where the model will include only data from the FAS biomarker positive population and include covariates using the IVRS data of treatment group, geographical region, age group, periostin group at baseline, and number of exacerbations in the year before the study, as described in Section 4.2.4.
- A Poisson regression model taking over-dispersion into account will be included as a sensitivity analysis for the primary analysis in the FAS (all subject population and the biomarker positive and negative populations). The correction for potential over-dispersion will be made by Pearson chi-square. The response variable, covariates and offset variables will be the same as in the primary analysis (Section 4.2.4).
- The interpretation of exacerbation data post-discontinuation of treatment is likely to be confounded by reduced quality of objective confirmation of deterioration, and by the use of subsequent therapies. Sensitivity analyses for the primary endpoint will be carried out to explore the impact of this. The primary analysis will be repeated, in the FAS (all subject population and the biomarker positive and negative populations), excluding data collected after discontinuation of IP.
- If there is a relevant imbalance in the baseline FE_{NO} values across the treatment groups, then an additional analysis of the primary endpoint will be performed in the FAS (all subject population and the biomarker positive and negative populations) including the baseline value as a continuous covariate in the analysis model.

- 



For variables with adjusted analysis-defined visit windows sensitivity analyses may be performed where observations are classified according to the extended windows described in [Table 3](#).

4.2 Analysis methods

4.2.1 Subject disposition, demography data and subjects characteristics

The subject disposition, demography data, and subject characteristics presentations will be presented for the all subject population and the biomarker positive and negative populations using the analysis sets as described below. In addition, demography data will also be presented for the FAS-Japan population.

Subject disposition will be summarised using the all subjects analysis set.

The number of enrolled subjects will be summarised. The number and percentage of subjects within each treatment group will be presented by the following categories; randomised, not randomised (and reason), received IP, did not receive IP (and reason), completed treatment discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason).

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented by treatment group and option of follow up (Section 1.2) and will also be listed.

Kaplan-Meier plots will be produced summarising the time (in days) to discontinuation of IP and withdrawal from the study.

Demographic data such as age, gender, and race will be summarised by treatment group for the FAS.

Various baseline characteristics will also be summarised by treatment for the FAS. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, FEV₁ (pre and post-BD) and FEV₁ reversibility at baseline, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalisations in the previous 12 months, phadiatop allergy test results, AQLQ(S) +12 at baseline and ACQ-6 at baseline. Baseline biomarker variables (periostin, DPP-4, FE_{NO}, eosinophils and IgE) will also be summarised by treatment for the FAS. Data collected at the latest pre-randomisation assessment will be summarised.

Medical and surgical histories will be summarised by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA.

4.2.2 Prior and Concomitant Medications

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by treatment for the FAS. Separate tables will be presented for all medications received during the following periods

- Prior: Medications with a stop date \leq the first day of IP.
- Concomitant - during treatment: Medications that are still ongoing on the first day of IP and also medications with start date \geq the first day of IP and \leq the last day of IP + 2 weeks.
- Post -treatment: Medications that are still ongoing one day after (the last day of IP + 2 weeks) and also medications with start date $>$ the last day of IP + 2 weeks and \leq Visit 31 (Week 72).

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose of ICS medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per patient from the first day of IP up to Week 52 will also be summarised.

A separate table will be presented for subjects who take disallowed concomitant medications. Disallowed medications will include medications defined as prohibited according to Appendix H of the CSP). They will be defined following a physician review (prior to database lock) of the unique combinations of ATC code classifications and generic terms captured.

Medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). Percentages will be calculated relative to the number of subjects in the FAS.

All medications will also be listed by subject for the FAS.

Data from subjects who discontinued IP, regardless of level of follow up chosen will, where possible and relevant, be included in the appropriate medication summaries.

4.2.3 Exposure and Compliance

Extent of exposure to IP is defined as the number of days between the start and the end dates of study therapy plus 14 days:

$$\text{Extent of exposure (days)} = (\text{Last dosing date} + 14 \text{ days}) - \text{First dosing date} + 1.$$

For subjects who withdraw from the study prior to the last dosing date+14 days, extent of exposure will be based on the date of withdraw from study rather than the dosing date +14 days.

In addition, the total number of dosing occasions will be calculated per subject.

Compliance is defined as:

$$\text{Compliance (\%)} = (\text{Total number of dosing occasions} / \text{total number of dosing occasions expected}) \times 100$$

Extent of exposure to IP, compliance, and total number of dosing occasions will be summarised by treatment group, for the all subject population and the biomarker positive and negative populations using the safety analysis set.

The date and time of IP administrations, and all missed doses will be listed using the safety analysis set.

Compliance with the regularly scheduled ICS/LABA asthma inhaler as recorded in the daily diary will be summarised by each bi-weekly period and treatment group, together with the compliance of the use of the daily diary.

4.2.4 Analysis of the primary variable

The primary efficacy variable is the AAER and the primary analysis is to compare the AAER for tralokinumab with placebo in the two subject populations based on the FAS (all subject population and the biomarker positive population). Analyses will also be repeated based on the biomarker negative population.

For each population the primary objective will be evaluated through the hypothesis test:

H_0 : rate ratio (tralokinumab/placebo) equals 1 vs.
 H_1 : rate ratio does not equal 1.

The null hypothesis (H_0) is that the exacerbation rate during the 52 week double-blind treatment period on tralokinumab is equal to the corresponding exacerbation rate on placebo. The alternative hypothesis (H_1) is that the exacerbation rate during the 52 week double-blind treatment period is different on tralokinumab compared with the exacerbation rate during the 52 week double-blind treatment period on placebo.

The AAER in the tralokinumab group will be compared to that seen in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a subject, over the 52-week double-blind treatment period. The model will include covariates using the IVRS data of treatment group, geographical region, age group, periostin group at baseline (with levels as defined in Section 1.2), and number of exacerbations in the year before the study. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term will be included in the model for the analysis of the biomarker populations only (the model for the all subjects population will not include these variables). The OM option will be used to adjust the co-efficients for the LSMEANS to reflect the observed data. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

The offset variables will be considered:

1. Logarithm of the number of days at risk of experiencing an exacerbation: follow-up time (follow-up date - date of randomisation + 1) minus the number of days the subject experiences a protocol defined exacerbation including the subsequent 7 days after each exacerbation (when a further exacerbation would not be considered as a second exacerbation) up to the follow-up date (i.e if an exacerbation ends 2 days prior to the follow-up date, the time of exacerbation plus 2 days (and not 7 days) will be subtracted from the follow-up time). This will be the definition included in the models used in the confirmatory analyses for primary and secondary objectives, as well as the sensitivity analyses defined in [Appendix B](#).
2. Logarithm of the follow-up time: follow-up date - date of randomisation + 1. This definition will be used in sensitivity analyses (see Section [4.1.2](#)).

Follow-up date is defined in Section [3.2.1](#).

The standard parameterization approach (NB2) of the Negative model will be applied ([Hilbe 2011](#)) using PROC GENMOD (SAS procedure).

The estimated treatment effect (i.e., the rate ratio of tralokinumab versus placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented. In addition, the AAER, the asthma exacerbation rate reduction, and the corresponding 95% CIs within each treatment group will be presented. Estimates (and 95% CI) based on marginal rates may also be presented to further explore treatment effects.

The individual exacerbation criteria (ER or UC visits due to asthma that required systemic corticosteroids, hospitalisation due to asthma, or use of systemic corticosteroids) will be summarised descriptively, and if appropriate (i.e. sufficient number of events) analysed using a similar model as for the primary variable.

4.2.4.1 Subgroup analyses

The consistency of treatment effect on the primary endpoint will be explored across different subgroups of the biomarker positive and negative populations. Subgroup analysis for the FAS (all subjects) will only be performed if there is a significant treatment effect for the annual exacerbation rate at week 52 in this population. For each subgroup separately, where sufficient data allows, a subgroup (if not already included) and a subgroup-by-treatment term as well as a 3-way biomarker population-by-subgroup-by-treatment interaction term will be added to the negative binomial model used in the primary analysis. The estimates (and 95% CIs) for the interaction effects, and estimates (and 95% CI) of treatment differences within each subgroup level will be reported. Subgroup analyses for evaluating eosinophils will include models excluding periostin baseline as a covariate. If there are issues with model convergence, then descriptive statistics by subgroup may be presented as an alternative. If there are subgroups with < 10 subjects per subgroup level, the exacerbation rate and rate ratio (including corresponding CIs) will be displayed as “NC” - not calculable; all data will be included in the analysis model.

Any subjects with a missing value for the defined subgroup will be excluded from the analysis of that subgroup.

The subgroups to be explored will include:

- Age by category: adults (>65), adults (≥ 18 to ≤ 65) and adolescents (≥ 12 to <18)
- ICS dose at study entry (medium, high) - Note: the process of categorizing ICS dose into these subgroups is detailed in a separate document (ICS Final v1.0).
- Eosinophils baseline group: <300/ μ L, $\geq 300/\mu$ L and <150/ μ L, $\geq 150/\mu$ L
- Geographical region (Asia Pacific [*incl. Japan, Philippines*], North America [*incl. Canada, US*], South America/Mexico [*incl. Chile, Mexico*], Central/Eastern Europe [*incl. Russia, Ukraine and Czech Republic*], Western Europe/Rest of the World [*incl. Italy, South Africa, UK*])
- Country - (for biomarker positive and biomarker negative populations summary statistics by country will be produced only)
- Race (as entered in the eCRF)
- Exacerbations in the year before study: ≤ 2 exacerbations, >2 exacerbations
- Chronic sinusitis and/or nasal polyps at baseline: yes, no

These analyses are exploratory and the results from these analyses will not affect the choice of terms used in the model for the primary analysis.

4.2.4.2 Supportive analysis of the primary variable using adjudicated data

A supporting analysis will be performed where exacerbations associated with hospitalisations and ER/UC visits that are adjudicated not to be asthma related are removed, and hospitalisations and ER/UC visit that are adjudicated to be asthma related are added, using the same negative binomial model as described in Section 4.2.4.

4.2.5 Analysis of key secondary variable(s)

All key secondary objectives will be analysed based on the FAS in both populations (all subject population and biomarker positive population) and in the biomarker negative population.

4.2.5.1 Lung Function

The key secondary outcome variable for lung function is: Percent change from baseline in pre-dose/pre BD FEV₁ at Week 52.

The percent change from baseline in pre-dose/pre-BD FEV₁ at Week 52 will be compared between tralokinumab and placebo using a restricted maximum likelihood (REML) based repeated measures analysis (using PROC MIXED in SAS).

All subjects with a baseline pre-dose/pre-BD FEV₁ measurement in the FAS will be included in the analysis. The dependent variable will be the percent change from baseline in pre-BD FEV₁ at post-baseline protocol-specified visits (up to the EOT visit). Fixed categorical effects of treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction will be included in the model and number of asthma exacerbations in the year prior to the study will be a fixed covariate in the model. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term and a 3-way biomarker population-by-treatment-by-visit interaction term will be included in the model for the analysis of the biomarker populations only (the model for the all subjects population will not include these variables). The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. Other variance-covariance structures may be considered if required. Further convergence issues may be resolved by using the PARMS statement within the PROC MIXED procedure to provide starting values for the covariance parameters (where values for the PARMS statement are obtained from a converged model including less data or omitting some of the covariates). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom, and the OM option will be used to adjust the co-efficients for the LSMEANS to reflect the observed data. The model for the biomarker positive population is:

*Percent change in FEV₁ = Treatment group + geographical region + age group + periostin group + number of asthma exacerbations in the year prior + visit + treatment*visit + biomarker population + biomarker population*treatment + biomarker population*treatment*visit*

Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% CIs and p-values. The treatment comparisons of primary interest for this variable will be the contrast between tralokinumab and placebo at Week 52, but estimates at all visits and overall will be presented.

Summary statistics for the percent change from baseline at all visits in pre-dose/pre-BD FEV₁ will be produced by treatment group.

Exploratory analysis of the consistency of the treatment effect on the percent change from baseline in pre-dose/pre BD FEV₁ at Week 52 across different subgroups will be explored based on the FAS biomarker positive and biomarker negative populations. Subgroup analysis for the FAS (all subjects) will only be performed if there is a significant treatment effect for the percent change from baseline in pre-dose/pre BD FEV₁ at Week 52 in this population. A separate model will be fitted for each category within the subgroups, as described in Section 4.2.4.1. For each model fitted, if the subgroup variable is included as a covariate in the model, then it will be excluded from the models for all categories of that subgroup. The estimates (and 95% CIs) for the interaction effects, and estimates (and 95% CI) of treatment differences within each subgroup level will be reported. If there are issues with model convergence, then descriptive statistics by subgroup may be presented as an alternative.

Supportive outcome variable: Absolute change from baseline in pre-dose/pre-BD FEV₁.

Absolute change from baseline in pre-dose/pre-BD will be analysed as described for the percent change on the FAS. Included in the model will also be the baseline pre-dose/pre-BD FEV₁.

Summary statistics for the absolute change from baseline at all visits in pre-dose/pre-BD FEV₁ will be produced by treatment group.

Other secondary outcome variable for lung function: Percent change from baseline in pre-dose/post-BD FEV₁

The percent change from baseline in pre-dose/post-BD FEV₁ will be analysed and summarised as described for the pre-dose/pre-BD FEV₁.

4.2.5.2 Asthma symptoms

The key secondary outcome variable: Change from baseline in bi-weekly mean daily asthma symptom total score (combined daytime and night-time score as captured in the Asthma Daily Diary).

The change from baseline in bi-weekly means (daily asthma symptom total score, daytime score, and night-time score) at Week 52 will each be summarised and analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline bi-weekly mean daily asthma symptom score.

The proportion of asthma symptom-free days up to Week 52 will also be summarised.

4.2.5.3 Asthma specific health-related quality of life

The key secondary outcome variable: Change from baseline in AQLQ(S) +12 total score.

The change in mean score from baseline for AQLQ(S) +12 at Week 52 (including the domain scores) will be summarised and analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline AQLQ(S) +12 total score.

Supportive outcome variable: AQLQ(S) +12 responder (yes/no)

Responder variables AQLQ(S)+12 (yes/no) will be analysed using a logistic regression model with responder at Week 52 as the response variable and covariates of treatment, geographical region, age group, periostin group, number of asthma exacerbations in the year prior to the study, and baseline AQLQ(S)+12 total score.

The number and percentage of subjects with AQLQ(S) +12 total score changes ≥ 0.5 will be summarised by treatment (identified as a large meaningful change). Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration will be summarised by treatment as per Section 3.3.6.

Supportive outcome variable: change from baseline to overall post-baseline mean of AQLQ(S) +12.

The change from baseline to overall post-baseline mean and the difference between treatments will be estimated from the repeated measures analysis described in Section 4.2.5.1.

4.2.5.4 ACQ-6 defined asthma control

The key secondary outcome variable: Change from baseline in ACQ-6

Change in mean score from baseline for ACQ-6 (and each of the individual questions) will be summarised and analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline ACQ-6 mean score.

Supportive outcome variable: ACQ-6 responder (yes/no).

Responder variables ACQ-6 (yes/no) will be analysed using a logistic regression model with responder at Week 52 as the response variable and covariates of treatment, geographical region, age group, periostin group, number of asthma exacerbations in the year prior to the study, and baseline ACQ-6 mean score.

The number and percentage of subjects achieving mean ACQ-6 ≤ 0.75 , $0.75 < \text{mean ACQ-6} < 1.5$ and mean ACQ-6 of ≥ 1.5 at Week 52 will be summarised by treatment. Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration as per Section 3.3.5, will also be summarised by treatment.

Supportive outcome variable: change from baseline to overall post-baseline mean of ACQ-6.

The change from baseline to overall post-baseline mean and the difference between treatments will be estimated from the repeated measures analysis described in Section 4.2.5.1.

4.2.6 Analysis of other secondary variables

All other secondary objectives will be analysed based on the FAS in both populations (all subject population and biomarker positive population) and in the biomarker negative population.

4.2.6.1 Proportion of subjects with ≥ 1 asthma exacerbation

The proportion of subjects with ≥ 1 asthma exacerbation during the 52 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion of subjects in the active tralokinumab arm will be compared with the proportion in the placebo group in both populations using a Cochran-Mantel-Haenszel test controlled for stratifying variables.

An odds ratio will be presented together with associated 95% CI and 2-sided p-value for tralokinumab versus placebo. The number and percentage of subjects with ≥ 1 asthma exacerbation will also be summarised by randomised treatment.

4.2.6.2 Time to first asthma exacerbation

Time to first asthma exacerbation will be analysed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with tralokinumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data including treatment, age group geographical region, periostin group at baseline, and number of exacerbations in the year prior to inclusion in the study as covariates, as well as a variable for biomarker population (positive, negative) and a biomarker population-by-treatment interaction term. Results of the analysis will be summarised as hazard ratios, 95% CIs and p-values.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot.

4.2.6.3 Emergency room or urgent care visits and hospitalisations due to asthma

AAER that are associated with an ER or UC visit or a hospitalisation will be analysed using a similar negative binomial model as outlined for the primary efficacy variable in Section 4.2.4

The response variable in the model will be the number of asthma exacerbations that are associated with an ER or UC visit or a hospitalisation experienced by a subject, over the 52-week double-blind treatment period. The model will include covariates of treatment group, geographical region, age group, periostin group at baseline, and number of exacerbations resulting in hospitalisation or ER treatment (yes/no) in the year before the study. A variable for the biomarker population (positive, negative) as well as a treatment-by-biomarker population interaction term will be included in the model for the analysis of the biomarker populations. The logarithm of the subject's corresponding time at risk of experiencing a new exacerbation defined as (Follow-up date - Date of randomisation + 1) minus the number of days the subject experiences a protocol defined exacerbation associated with an ER or UC visit or a hospitalisation including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation) will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

Supportive outcome variable: Emergency room or urgent care visits and hospitalisations due to asthma using adjudicated data

A supporting analysis will be performed where exacerbations associated with hospitalisations and ER/UC visits that are adjudicated not to be asthma related are removed, and hospitalisations and ER/UC visits that are adjudicated to be due to an asthma exacerbation are added. The same negative binomial model as described above will be used. Any discrepancies between the secondary analysis and this supporting analysis will be tabulated.

4.2.6.4 Health care resource utilization and productivity loss due to asthma

The total number events/days will be presented by treatment along with descriptive statistics for the treatment period mean per subject, for all variables listed in Section 3.3.8.

Health care resource utilization data will be combined with economic data collected independently of the study to construct comparative health economic analyses between treatment groups. These analyses will be reported separated from the main study report.

4.2.6.5 WPAI-CIQ

For each time point at which the WPAI-CIQ is administered, descriptive statistics by treatment will be presented, as described in Section 3.3.9.

Work productivity loss data will be combined with economic data collected independently of the study to construct comparative health economic analyses between treatment groups. These analyses will be reported separated from the main study report.

4.2.6.6 Nights with awakening due to asthma

The change from baseline in the bi-weekly mean number (percentage) of nights with awakening due to asthma that required rescue medication will be analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline bi-weekly mean number (percentage) of nights with awakening due to asthma that required rescue medication.

4.2.6.7 Rescue medication use

The change from baseline in bi-weekly mean rescue medication use will be summarised and analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline mean rescue medication use.

The number and percentage of subjects within each treatment group who received rescue medication will be summarised by each bi-weekly period.

4.2.6.8 Home PEF (morning and evening)

The change from baseline in bi-weekly mean morning and evening PEF will each be summarised and analysed using the repeated measurement approach defined for percent change from baseline in pre-dose/pre-BD FEV₁, as described in Section 4.2.5.1. Included in the model will also be the baseline morning and evening PEF.

4.2.6.9 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L responses from each dimension and the visual analogue scale will be summarised by treatment group. The number and percentage responses to each dimension will be summarised by assessment, and shift tables for baseline to Week 52 will be presented for each dimension. The mean and mean change from baseline to each assessment in VAS will be summarised with descriptive statistics.

Utility derived from EQ-5D will be calculated to construct comparative health economic analyses between treatment groups. These analyses will be reported separate from the main study report.

4.2.7 Safety and tolerability

All safety variables will be summarised using the safety analysis set in both populations (all subject population and biomarker positive population) and in the biomarker negative population. Data will be presented according to treatment received.

4.2.7.1 Adverse events

AEs will be summarised separately for the treatment and study periods defined in Section 3.4.1. AEs occurring during the run-in period, or occurring post-treatment (as per Section 3.4.1) will be listed, but not summarised separately.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE in any of the following categories: AEs, serious adverse events (SAEs), deaths due to AE, AEs causing discontinuation of IP (DAEs), and other significant adverse events (OAEs). OAEs will be defined following medical review of system organ classes/preferred terms after unblinding of the data. The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e., accounting for multiple occurrences of the same event in a subject).

AEs will be summarised by SOC and PT assigned to the event using MedDRA. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented i.e., for a subject multiple occurrences of an AE will only be counted once.

AEs (by SOC and PT) will be summarised by causality and maximum intensity. If a subject reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity for each SOC and PT (the order being mild, moderate, and severe).

The following will also be summarised by SOC and PT

SAEs

AEs in the category of safety topics of special attention

DAEs

DAEs causally related to IP

SAEs leading to discontinuation of IP

Most common AE's (frequency of >3%) (by PT only)

Deaths

Injection site reactions will be reported by preferred term for the treatment period, summarised by treatment group.

The approach to identifying possible anaphylaxis/hypersensitivity AEs occurring within 3 days of IP administration is described in a separate charter. Those identified AEs meeting the criteria described in this charter will be summarised by preferred term and treatment group for the treatment period and study period.

Subjects experiencing a severe infection are defined as having an AE which met one of the following:

- life-threatening,
- requiring hospitalisation,
- requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infections,
- permanent discontinuation of study drug.

Severe infections will be summarised by MedDRA high level group term, high level term and preferred term by treatment group for the treatment period and study period.

A summary of AEs by SOC and PT for subjects with at least one post-baseline eosinophil value $> 1500/\mu\text{L}$ may be produced if there is an imbalance between treatment groups in the number of subjects with post-baseline eosinophil values $> 1500/\mu\text{L}$.

The rate of AEs per person-years at risk, calculated as (number of subjects reporting AE)/(total time at risk of AE), will also be reported for the treatment period. Rates will typically be expressed in terms of events per 100 subject-years. Total time at risk will be defined as (the date of last day of IP + 2 weeks) - date of randomisation + 1.

Separate listings of subjects with AEs, SAEs, death due to AE, or discontinuations due to AEs will be presented.

Adjudicated events (MACE (major adverse cardiac events) and malignancies) will be summarised by treatment group and listed.

4.2.7.2 Laboratory data

All continuous laboratory parameters will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group.

Central laboratory reference ranges will be used for the identification of individual clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum on-treatment values, as applicable for each parameter.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. A diagonal line indicating no change, and horizontal and vertical reference lines indicating the limits of the reference ranges will also be displayed on the shift plots.

The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (using reference ranges) occurring during the clinical study will also be given. In addition, the number of subjects with a post-baseline eosinophil value of $>1500/\mu\text{L}$ will be presented by treatment group.

In order to identify potential Hy's Law cases, maximum post baseline TBL will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline TBL against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for total bilirubin and at 3xULN for ALT/AST.

For all subjects who meet the biochemical criteria for Hy's law (potential Hy's Law), a Subject Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST, and elevated TBL, at any time may be explored further graphically using individual subject profile plots.

For urinalysis data, a shift table will be generated to present changes from baseline to last observation in the on-treatment period (using the 'during treatment' definition as in Section 3.4.1). The number of subjects with treatment-emergent changes will also be summarised. Here, treatment-emergent changes are defined as None/Trace at baseline to Positive, at any visit after baseline.

Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.

4.2.7.3 dECGs

The Investigator's assessment of the 12-lead dECG (normal or abnormal) will be listed for all subjects, along with detailing whether any abnormalities were clinically significant or not.

The number and percentage of subjects with clinically significant abnormal dECGs will be summarised by treatment group and visit.

4.2.7.4 Physical Examination

Shift tables (normal, abnormal (same as Visit 1, new or aggravated) of Visit 1 versus last observation during treatment (as defined in Section 3.4.1) will be generated, presenting the assessment for each component of the complete physical examination separately.

A similar shift table (normal, abnormal) of baseline (typically Visit 3) versus the last observation during treatment will also be generated.

Listings of results will be produced, including the date of assessments of the brief physical exam.

4.2.7.5 Vital Signs

All vital signs parameters will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

AstraZeneca defined reference ranges will be used for the identification of individual abnormalities, and a shift table will be produced for each vital signs parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum during treatment value, as applicable for each parameter.

Shift plots showing each individual subject's vital signs value at baseline and at maximum/minimum will be produced for each continuous vital signs parameter.

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented, using AstraZeneca clinically important change criteria. This data presentation will include all visits for each parameter with treatment-emergent changes for this subset of subjects. A change is treatment-emergent if it occurred during treatment, using the same definition as in Section 3.4.1

All recorded vital signs data will be listed.

4.2.7.6 Weight and BMI

Weight, BMI and height (for adolescents only) will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline.

4.2.7.7 Analysis of Immunogenicity variables

ADA status (positive vs. negative) at each visit will be summarised by treatment group. Descriptive statistics including number of subjects, mean, standard deviation, median, and range of the actual ADA titres by treatment group and visit, where possible, will be provided. The ADA status across the study for each subject will also be classified and summarised by treatment group. The association of ADA status across the study with AEs/SAEs and exacerbation data may be evaluated. In addition, the association of ADA titres (\geq median titre in positive subjects vs. $<$ median titre) with AE/SAEs may be evaluated for ADA-positive treated subjects only. The following ADA results will be evaluated as proportion of subjects in cohorts together with corresponding titre summaries. However, if the number of ADA positive subjects in the safety analysis set is small then the ADA variables may be listed only in the CSR and the analysis of immunogenicity variables performed outside of the CSR based on pooled data from STRATOS 1 and STRATOS 2.

- Subjects who are ADA positive at any time (including baseline).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are positive at baseline regardless of post-baseline result.

- Subjects who are ADA positive post-baseline.
- Subjects who are ADA positive post-baseline and ADA negative at baseline.
- Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements or an ADA positive result at the last available assessment.
- Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Subjects who are ADA positive by visit.
- Subjects who are ADA positive at a post-baseline measurement for the first time by visit.
- Subjects who are ADA positive within the Placebo group at any time.

For ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titre summary will be based on the titre of the positive sample for that particular visit.

For proportions summarising across visits (e.g. any ADA post-baseline) the corresponding titre summaries will be based on the maximum titre of all positive samples for each subject.

The ADA-positive subjects across the study may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADAs for at least two consecutive visits (with ≥ 16 weeks between the first and last positive value), or positive at the last post-baseline visit. Otherwise, the subject will be considered as transient ADA positive. The associations between ADA and AE/SAEs may be summarised for both persistent positive subjects versus transient positives subjects.

The presence of neutralizing antibodies (nAb) will be tested in all post-dose ADA-positive samples using a ligand binding assay.

Neutralizing ADA evaluations will be conducted on confirmed ADA positive samples. The test sample is deemed positive or negative for the presence of nAb to talokinumab relative to a pre-determined (in assay validation), statistically derived cut point. The following variables will be evaluated:

- Proportion of ADA positive subjects who are nAb positive at any time.
- Proportion of ADA positive subjects (at any time) who are nAb positive for the first time by visit.
- Subjects who are persistently nAb positive; persistently positive is defined as at least 2 post-baseline nAb positive measurements.

Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline nAb positive measurement and not fulfilling the conditions for persistently positive sample. For ADA, all subjects will be shown in the data listing.

4.2.8 Analysis of pharmacokinetics

All analyses of PK variables will be based on the PK analysis set, all analyses on immunogenicity variables will be based on the safety analysis set.

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed serum trough (predose) concentrations, C_{trough} . If possible and if relevant, empirical evaluation of potential impact of demographic covariates and ADA on C_{trough} may be conducted.

For descriptive statistics of C_{trough}

- if, at a given time point, 50% or less of the concentrations are non-quantifiable (NQ), the geometric mean, coefficient of variation (CV), arithmetic mean and SD will be calculated by substituting the lower limit of quantification (LLOQ) divided by 2 for values which are NQ.
- if more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, arithmetic mean and SD will be reported as not calculable (NC)
- if all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV and SD as NC
- the median, minimum and maximum will also be reported.

The LLOQ of tralokinumab in serum will be 0.100 µg/mL.

The PK data may be merged with those from other clinical studies for a population-based meta-analysis. If performed, results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR.

4.2.9 Exploratory analyses

4.2.9.1 Baseline FE_{NO} levels as predictive biomarker

The utility of subject's baseline FE_{NO} as a predictive continuous biomarker for treatment effect on asthma exacerbation rate and asthma symptom control will be explored, using a number of analyses:

- Graphical presentation of models assessing and characterizing the relationship between exacerbation rate and baseline FE_{NO} value by treatment group; including
 - Scatterplots (with a graphical representation of a negative binomial model fitted as described in Section 4.2.4, including covariates for treatment group, geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study. A variable for FE_{NO} will be included

as a continuous variable as well as a treatment-by FE_{NO} interaction term. If the p-value for the interaction term <0.1, then this would be considered indicative of a predictive biomarker.

- A likelihood ratio test to assess whether FE_{NO} generally have predictive properties of the tralokinumab treatment effect. The test will compare a model with only treatment, baseline variables (geographical region, age group, periostin group at baseline and number of exacerbations in the year before the study) and continuous FE_{NO} as covariates to a model that also includes a FE_{NO}-by-treatment interaction term.

A cutoff of 37 ppb has been chosen based on STRATOS 1, however there is no one value on the FE_{NO} scale where there is a step change in effect. As such the following supportive analyses will be produced to assess a range of alternative thresholds. These methods include

- Cumulative cut-off plots
- AERR for biomarker positive population as threshold ranges from 30 to 42 ppb
- Summaries of key secondary endpoints for biomarker positive population for thresholds of 32 and 42 ppb.

All the negative binomial models used in the above analyses will, in addition to the biomarker terms, include the same covariates as the primary analysis model of the biomarker populations.

Other biomarkers that may be associated with up-regulation of IL-13 will be explored in a separate report outside of the CSR.

4.2.9.2 Biomarkers associated with up-regulation of IL-13

The change from baseline in biomarkers that may be associated with up-regulation of IL-13 e.g. IgE, eosinophils, FE_{NO} will be explored. Summary statistics and graphical presentations of change from baseline to each assessment will be presented for each biomarker. Possible correlation between biomarker and clinical efficacy will be explored graphically. As FE_{NO} has been selected as the biomarker to define the biomarker positive population, no post-baseline periostin and DPP-4 data will be available for analysis.

[REDACTED]

5. INTERIM ANALYSES

No interim analysis is planned for this study.

The exacerbation rate and dispersion will be monitored in a blinded fashion during the execution of the study. If the blinded estimate of the exacerbation rate and/or dispersion indicates that the assumptions in the power calculation are incorrect, appropriate analyses (blinded) will be undertaken to investigate this further. The result of these analyses may lead to an increase in sample size. Any decision to increase the sample size will be taken when sufficient data is collected but before last subject has been randomised in the study. The analyses will be performed by AstraZeneca.

An independent Adjudication Committee, blinded to the treatment of the subjects, will evaluate cases of ER or UC visits and hospitalisations, as well as all deaths, to determine whether they are due to asthma or not. The adjudication committee will also review MACE and malignancies occurring after randomisation

An independent Data and Safety Monitoring Board (DSMB) will safeguard the interest of adolescent subjects by assessing the safety of the intervention. The DSMB will review safety data on a regular basis as set out in a DSMB charter. The data for review will be outlined in a DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. For reference, the DSMB will also have access to study data from adults.

An independent review of all potential anaphylaxis/hypersensitivity events will be performed by a clinical expert (external to AZ). Results from the external review will be included in the CSR addendum. Further details of the identification and review process are contained in the Hypersensitivity and Anaphylaxis Process Charter.

6. CHANGES OF ANALYSIS FROM PROTOCOL

A number of clarifications and minor corrections have been made and are listed below:

- 4.2.6.1: updated to detail that odds ratio, rather than weighted difference will be presented
- 3.3.2/3.3.3/4.2.6.6/4.2.6.7: clarification added that change from baseline for rescue medication will be summarised and analysed.
- 3.1.1: clarification of baseline for the diary variables added

7. REFERENCES

Hilbe 2011

Hilbe J. M. (2011) “Negative Binomial Regression” Cambridge University Press
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Keene et al 2007

Keene ON, Jones MRK, Lane PW, et al. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharm Stat 2007;6:89-97.

Appendix A Analysis Windows for EQ-5D

Table 7 Analysis windows for EQ-5D

Visit	Target Day	Adjusted windows for weekly measures
Baseline (Week 0) ^a	1	1
Week 1	8	2-11
Week 2	15	12-18
Week 3	22	19-25
Week 4	29	26-32
Week 5	36	33-39
Week 6	43	40-46
Week 7	50	47-53
Week 8	57	54-60
Week 9	64	61-67
Week 10	71	68-74
Week 11	78	75-81
Week 12	85	82-88
Week 13	92	89-95
Week 14	99	96-102
Week 15	106	103-109
Week 16	113	110-116
Week 17	120	117-123
Week 18	127	124-130
Week 19	134	131-137
Week 20	141	138-144
Week 21	148	145-151
Week 22	155	152-158
Week 23	162	159-165
Week 24	169	166-172
Week 25	176	173-179
Week 26	183	180-186
Week 27	190	187-193
Week 28	197	194-200
Week 29	204	201-207
Week 30	211	208-214
Week 31	218	215-221
Week 32	225	222-228
Week 33	232	229-235

Table 7 Analysis windows for EQ-5D

Visit	Target Day	Adjusted windows for weekly measures
Week 34	239	236-240
Week 35	246	241-249
Week 36	253	250-256
Week 37	260	257-263
Week 38	267	264-270
Week 39	274	271-277
Week 40	281	278-284
Week 41	288	285-291
Week 42	295	292-298
Week 43	302	299-305
Week 44	309	306-312
Week 45	316	313-319
Week 46	323	320-326
Week 47	330	327-333
Week 48	337	334-340
Week 49	344	341-347
Week 50	351	348-354
Week 51	358	355-361
Week 52	365	362-368

^a If the Day 1 assessment is missing, see Section 3.1.1 on how baseline value is defined.

Appendix B Accounting for Missing Data

To minimise the amount of missing data in the study subjects are encouraged to remain in the study after premature discontinuation of IP and complete visits according to the protocol. However, subjects dropping out of the study will potentially lead to unobserved events and measurements.

This section summarises how we will describe the pattern of and reasons for missing data from the study. It will also describe how we plan to account for missing data, including both the primary and sensitivity analyses to assess the robustness of the treatment effect under different underlying assumptions to account for missing data.

The analysis described will be performed for the FAS (all subject population and the biomarker positive and negative populations).

Accounting for missing data for recurrent events (exacerbation rate endpoint)

Missing data descriptions

Tabular summaries for the percentage of subjects by the reason for discontinuation of randomised treatment as well as for withdrawal from the study will be presented by treatment to describe why subjects discontinue from randomised treatment or withdraw from the study. The time to discontinuation of randomised treatment and withdrawal from the study by treatment will be presented using Kaplan Meier plots. Since the imputation methods presented below are based on reason for discontinuation and withdrawal, the plots will also be split by treatment related/not treatment related reason for discontinuation (as defined in [Table 8](#) and [Table 9](#)). Dependent on these outputs additional exploratory analyses may be produced as deemed necessary to further understand the pattern of missing data.

Primary analysis under the Treatment Policy Estimand using the Missing at Random (MAR) assumption

The primary analysis is under the treatment policy estimand, which implies the inclusion of all data until subjects withdraw from the study regardless of if they discontinue from randomised treatment. This allows for differences in outcomes over the entire study treatment period to reflect the effect of initially assigned randomised treatment as well as if subsequent treatments are taken. The primary analysis uses the negative binomial regression model with (logarithm of) the time at risk of experiencing an exacerbation (as defined in [Section 4.2.4](#)) as an offset term and assumes that missing data is MAR, and will be applied where all of the available observed data are analysed without deletion nor imputation. This is a so called direct likelihood approach (DL).

Sensitivity analyses under the Treatment Policy Estimand using both MAR and MNAR assumptions

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional analyses will be performed using the controlled multiple

imputation method introduced in [1] and further developed and assessed at AstraZeneca [2, 3]. As with the primary analysis, the sensitivity analyses includes all data until subjects withdraw from the study regardless of if they discontinue from randomised treatment.

For this method, post study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal, a post-withdrawal model assumption, the baseline covariates included in the primary analysis model and the time remaining after discontinuation to end-of study (52 Weeks).

The method involves first fitting the primary analysis i.e. negative binomial regression model to the observed data and drawing independent samples from the joint distribution of the model parameters, creating a number of parameter sets that consist of the linear regression terms and the log of the dispersion parameter. It is assumed that the dispersion parameter is asymptotically independent of the other model parameters. This distribution is approximately the same as the posterior distribution for the parameters of a Bayesian log-linear negative binomial model with non-informative priors.

Imputed post-withdrawal counts are then generated for each discontinued subject by, for each generated set of model parameters, drawing a random number from the probability function for post-withdrawal counts, conditioned on the observed number of events prior to withdrawal for that subject. The conditional distribution for subject i is a negative binomial distribution with probability of event p_j and dispersion parameter $\gamma + y_i$, where y_i is the number of counts before withdrawal from the study, γ is the dispersion parameter estimated from observed data. The j denotes the treatment arm. Furthermore,

$$p_j = \frac{p_{j,1} - p_{j,1} p_{j,2}}{1 - p_{j,1} p_{j,2}} \quad (1)$$

where $p_{j,1}$ is the negative binomial distribution parameter for probability of event before withdrawal from the study, and $p_{j,2}$ is the corresponding post withdrawal parameter determined by various assumptions and the baseline covariates included in the primary analysis model (the intensity λ_j is $p_j / (1 - p_j)$)

The imputed number of exacerbations is then combined with the observed exacerbations and data is analysed using the primary analysis methodology. This analysis is repeated multiple times and the results combined using Rubin's formulae [7,8].

The following assumptions that will be used to determine $p_{j,2}$ and impute the missing data who withdraw early from the study:

- (a) MAR: Missing counts for a subject is imputed using the observed event rate within the treatment group of that subject ($p_{j,2} = p_{j,1}$).
- (b) Dropout Reason-based Multiple Imputation (DRMI): Missing counts will be imputed differently depending on the reason for dropout; counts for subjects in the Tralokinumab arm who dropped out for a treatment related reason are imputed based on the expected event rate in the placebo arm ($p_{T,2} = p_{P,1}$), whereas the

remaining subjects who have dropped out are imputed assuming MAR. Treatment related reasons include (1) AEs, (2) Death and (3) development of study specified reasons to stop active treatments, (4) severe non-compliance of protocol.

Together with the primary analysis these sensitivity analyses are considered to cover the range from realistic to plausible worst case assumptions about missing data. The MAR multiple imputation approach is expected to correspond closely to the primary analysis, and is included to allow for comparisons with MNAR assumptions (specifically method b) using the same multiple imputation methodology

The dropout reason-based multiple imputation (DRMI) approach was selected as the most conservative approach based on the fact that placebo subjects are receiving standard of care and are not expected to change to a substantially more effective treatment after withdrawing from study or study treatment. For subjects receiving Tralokinumab who withdraw from the study due to treatment related reasons it is assumed that at worst they would be on the standard of care treatment i.e. the placebo arm. For subjects receiving Tralokinumab who withdraw from the study due to non-treatment related reasons it seems reasonable to assume they would be similar to those subjects who complete treatment.

Some reasons for withdrawal are clearer to define as treatment related (*Adverse Events, Death, Development of study-specific discontinuation criteria*) or non-treatment related (*Subject lost to follow up, eligibility criteria not fulfilled*). Other reasons are less clear such as subject decision and 'Other'; a review of each subject who withdraws from the study will therefore be carried out prior to unblinding the study. The review will include assessment of the reason for discontinuation of randomised treatment for those subjects who discontinued randomised treatment and then withdrew from the study and also free text for when the reason for withdrawal or discontinuation of randomised treatment is subject decision or other. Based on this review the default assumptions for DRMI as described in b) and [Table 8](#) may be changed. A list of these subjects and the assumptions made under DRMI will be documented prior to unblinding of the study.

A summary of reasons for subjects withdrawing from the Tralokinumab treatment arm and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI is given in [Table 8](#).

Table 8 Treatment arms used to calculate imputation rate, by reason for withdrawal

Reason for withdrawal	MAR	DRMI
Adverse Event	Tralokinumab	Placebo
Development of study-specific discontinuation criteria*	Tralokinumab	Placebo
Death	Tralokinumab	Placebo
Severe non-compliance to protocol	Tralokinumab	Placebo
Eligibility criteria not fulfilled	Tralokinumab	Tralokinumab
Subject lost to follow up	Tralokinumab	Tralokinumab
Subject decision	Tralokinumab	Based on review prior to study unblinding
Other	Tralokinumab	Based on review prior to study unblinding

Note: All subjects on exacerbation rate in the placebo arm are imputed using the placebo arm rate

*Development of study-specific discontinuation criteria are based on the following: anaphylactic reaction to the IP requiring administration of epinephrine, development of helminth parasitic infestations requiring hospitalisation, intensive care unit admission for asthma-related event, malignancy.

In addition, a tipping point analysis may be performed using the same model as above; Missing counts for a subject will be imputed, according to the rate of the arm that the subject belongs to multiplied by a factor delta (p_j is calculated using the MAR assumption and then the imputation rate is calculated as $\lambda_j^* = \delta_j \lambda_j$).

A series of analyses will be performed with a range of increasing deltas for the two arms (δ_P and δ_T for placebo and tralokinumab group respectively) so that one could assess at which point the study conclusions would change from favourable to unfavourable; i.e., to identify a tipping point.

In this assessment, the placebo group is assumed to improve after withdrawal and the tralokinumab group is assumed to worsen after withdrawal. Therefore, $\log(\delta_P)$ will be varied from -1.5 to 0 in increments of 0.5 and $\log(\delta_T)$ will be varied from 0 to 1.5 in increments of 0.5. This corresponds to deltas between 0.22 and 1 for the placebo group and deltas between 1 and 4.5 for the tralokinumab group. If statistical significance ($p \leq$ the alpha level used according to the testing strategy described in Section 4.1.1) is maintained among the matrix of possible δ combinations, the comparison is deemed robust to missing data. For a given comparison, if a tipping point was observed with analysis at 0.5 increments, the δ values will be further refined down to 0.25 increments for the relevant interval. For example if a tipping point is identified when increasing $\log(\delta_T)$ from 1 to 1.5, the matrix will be expanded to include also the value $\log(\delta_T) = 1.25$.

On-Treatment Analyses (Efficacy and Effectiveness estimands)

In addition primary and sensitivity analyses described previously, two alternative estimands will be estimated using only the on initial randomised treatment data:

- Efficacy estimand - what would have been the outcome if all subjects had stayed on study treatment: This will be estimated using the primary analysis method but including only data from subjects whilst being on initial randomised treatment, and assuming MAR subsequently.
- Effectiveness estimand with assumed loss of effect post discontinuation of Tralokinumab: This will be estimated using the DRMI controlled imputation approaches including only data from subjects whilst on treatment.

Therefore the primary analyses and sensitivity analyses will be repeated including only data from subjects whilst being on initial randomised treatment i.e. excluding data once subjects discontinue from randomised treatment.

A summary of reasons for subjects withdrawing from the Tralokinumab treatment arm and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI are given in Table 9. As for subjects who withdraw from the study, a review of each subject who discontinued randomised treatment will be carried out prior to unblinding the study where the default assumptions for DRMI as described in Table 9 may be changed. Again a list of these subjects and the assumptions made under DRMI will be documented prior to unblinding of the study.

Table 9 Treatment arms used to calculate imputation rate, by reason for discontinuation of treatment

Reason for discontinuation of IP	MAR	DRMI
Adverse Event	Tralokinumab	Placebo
Development of study-specific discontinuation criteria*	Tralokinumab	Placebo
Severe non-compliance to protocol	Tralokinumab	Placebo
Subject lost to follow up	Tralokinumab	Tralokinumab
Subject decision	Tralokinumab	Based on review prior to study unblinding
Other	Tralokinumab	Based on review prior to study unblinding

Note all subjects on exacerbation rate in the placebo arm are imputed using the placebo arm rate

*Development of study-specific discontinuation criteria are based on the following: anaphylactic reaction to the IP requiring administration of epinephrine, development of helminth parasitic infestations requiring hospitalisation, intensive care unit admission for asthma-related event, malignancy.

Using on treatment data is easier to interpret as it is not impacted by any subsequent pattern of alternative treatments once subjects discontinue from randomised treatment. The efficacy estimand together with the reason for and timing of why a subject might not tolerate the treatment allows for the simplest interpretation as it describes the treatment effect for subjects who adhere to treatment together with why and when they might not adhere to treatment. Sensitivity analyses using the effectiveness estimands under DRMI allow for alternative assumptions to be made based on reasons for discontinuation.

Overall summary of analyses to account for missing data

A summary of the different analyses to be carried out under different estimands and assumptions are described in [Table 10](#).

Table 10 Summary of analyses by estimands

	Treatment Policy Estimand			On-Treatment Analyses (Efficacy and Effectiveness estimands)		
	DL	MAR	DRMI	DL	MAR	DRMI
Population	On-treatment + post-discontinuation of randomised treatment					
Estimand	Treatment policy (MAR)	Treatment policy (MNAR)		On-treatment		
				Efficacy (MAR)		Effectiveness (MNAR)
Exacerbation rate for imputation in Tralo arm**	No explicit imputation*	Tralo rates for all reasons for withdrawal	Placebo rate for AE, Death, development of study specified reasons to stop active treatments and Severe non-compliance to protocol, otherwise Tralo or based on review prior to study unblinding	No explicit imputation*	Tralo rate for all reasons for withdrawal	Placebo rate for AE, development of study specified reasons to stop active treatments and Severe non-compliance to protocol, otherwise Tralo or based on review prior to study unblinding
Definition for $p_{j,1}$ and $p_{j,2}$ in formula (2) ****.		$p_{j,2} = p_{j,1}$ For all treatment arms j=T and P	$p_{T,2} = p_{T,1}$ for reasons above otherwise $p_{T,2} = p_{P,1}$ $p_{P,2} = p_{T,1}$		$p_{j,2} = p_{j,1}$ For all treatment arms j=T and P	$p_{T,2} = p_{T,1}$ for reasons above otherwise $T = p_{P,1}$ $p_{P,2} = p_{P,1}$

* Implicitly assumes unobserved rate the same as observed

** All subjects on exacerbation rate in the placebo arm are imputed using the placebo arm rate (i.e. $p_{P,2} = p_{P,1}$)

*** P denotes Placebo, T denotes Tralokinumab

**** Note can be over written by review prior to study unblinding

Forest plots will be used to show the primary analysis results along with the missing data sensitivity and alternative estimand analysis results.

It is noted that if the primary analysis is statistically significant, it is not necessarily expected that all sensitivity analyses will also give statistically significant results. If the results of the sensitivity analyses provide reasonably similar estimates of the treatment effect to the primary analysis, this will be interpreted as providing assurance that neither the lost information nor the mechanisms which cause the data to be missing have an important effect on primary analysis conclusions. Based on these outputs and the drug's mechanism of action, the plausibility of the assumptions we make about missing data in the different analyses will be considered and described in the clinical study report.

Accounting for missing data for selected continuous key secondary endpoints (Percent change from baseline in pre-dose/pre-BD FEV1 and Change from baseline in AQLQ(s)+12 at Week 52)

Sensitivity analyses of change from baseline in bi-weekly mean daily asthma symptom score and change from baseline in ACQ-6 total score may be available if requested. These will be using the same approaches as specified below.

Missing data descriptions

In addition to the tables and figures suggested above, plots of change from baseline vs time, by dropout pattern (e.g. completers vs non-completers, split by reason for dropout and/or split by last available visit) will also be produced.

Primary analysis under the Treatment Policy Estimand using the MAR assumption

As for the primary variable, the primary analysis of the continuous key secondary endpoints includes all data captured during the trial and is therefore considered to be under the treatment policy estimand. The Mixed Model Repeated Measures model (MMRM) used is a DL approach which is valid under the MAR assumption.

Sensitivity analysis under the Treatment Policy Estimand using MNAR assumptions

Sensitivity analyses of the repeated measures analyses will be performed for the continuous key secondary endpoints using controlled sequential multiple imputation methods based on pattern mixture models, as described in [8].

The method is analogous to the multiple imputation of exacerbation events and the imputation process consists of a sequence of MI steps, where each step is intended to impute missing values at one time-point only. This model will assume that some pre-specified subset of subjects who withdraw from the study have correlations with future (unobserved) visits similar to subjects in the placebo arm. As for the exacerbation events, this allows us to assess various deviations from the MAR assumption.

The assumptions that will be used to impute the missing data who withdraw early are as follows:

- (a) MAR: Assumes that the trajectory for subjects who dropped out in each arm is similar to those observed in their own treatment arm
- (b) DRMI: Assumes that the trajectory for subjects in the Tralokinumab arm who dropped out for treatment related reasons (according to the same classification as for the DRMI analysis of the primary endpoint) is similar to that of the placebo subjects, whereas the remaining subjects who has dropped out are imputed assuming MAR.

Approach b) can be considered more conservative than the approach for the primary analysis because the assumptions mean that as soon as subjects withdraw for a treatment related reason, they begin to worsen immediately.

Imputation will be done in two steps, the non-monotone (intermediate) missing values will be imputed first (Markov chain Monte Carlo (MCMC) method is used to partially impute the data using SAS PROC MI) and then the missing value at each visit will be imputed using a sequential regression method (using MONOTONE REG option of SAS PROC MI). The imputation model will include the baseline covariates used in the primary analysis model.

The MNAR imputation is achieved by only including selected data at each stage of the imputation. For example, to impute missing values at time t for subjects in the Tralokinumab arm, that dropped out for treatment related reasons, include only placebo observations up to and including time t , plus observations from subjects in the Tralokinumab arm, that dropped out for treatment related reasons, up to and including time $t-1$. This is done for each visit, one at a time using observed data. Placebo missing observations and Tralokinumab observations that are not missing for treatment related reasons are imputed assuming MAR and follow the pattern of observed placebo observations in each treatment arm respectively. 100 imputations will be carried out, and a seed of 784478 will be used.

The imputation models will be based on absolute values (including the baseline value) and change from baseline will be calculated in imputed datasets. The analysis of each of these imputed datasets will be as described for the primary analysis in Section 4.2.4, and these will be combined using SAS procedure PROC MIANALYZE.

In addition, a tipping point analysis may be performed using the same methodology as above; subjects who withdrew from the study will have their first imputed efficacy score worsened by some amount δ . This results in a one-time shift towards a worse value in the outcomes of subjects that withdrew from the study after a given visit. Again, a series of analyses will be performed with a range of increasing deltas for the two arms (δ_P and δ_T for placebo and tralokinumab group respectively) to identify a tipping point.

In this assessment, the placebo group is assumed to improve after withdrawal and the tralokinumab group is assumed to worsen after withdrawal. Therefore, for FEV₁ δ_P will be varied from 0 to 300ml in increments of 100ml and δ_T will be varied from 0 to -300ml in

increments of 100ml. If statistical significance ($p \leq$ the alpha level used according to the testing strategy described in Section 4.1.1) is maintained among the matrix of possible δ combinations, the comparison is deemed robust to missing data. For a given comparison, if a tipping point was observed with analysis at 100 increments, the δ values will be further refined down to 50ml increments for the relevant interval. For example if a tipping point is identified when increasing δ_T from -300ml to -200ml, the matrix will be expanded to include also the value $\delta_T = -250$ ml.

Similarly for the AQLQ score, δ_P will be varied from 0 to -3 in increments of -1 and δ_T will be varied from 0 to 3 in increments of 1.

On-Treatment Analyses (Efficacy and Effectiveness estimands)

Analogously to the approach for the primary endpoint, efficacy and effectiveness estimands will be estimated using on-treatment data and the methods described above.

Results for continuous endpoints will be presented as per the recurrent event sensitivity analyses

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